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5.3.6 Post-Marketing Adverse Drug Event Experience(s) Report Description

Periodic Adverse Drug Experience Report for Indomethacin ER Capsules, USP 75 mg encompasses the reporting period of 06-Mar-2024 through 05-Mar-2025.

In accordance with the provisions of 21 CFR 314.80(c)(2), Post-Marketing Reporting of Adverse Events, Avanthi, Inc. reports that there were Two (2) 15-Day Alert Reports and Zero (0) Non-15-Day Reports for Indomethacin ER Capsules, USP 75 mg: ANDA # 079175 during the reporting period 06-Mar-2024 through 05-Mar-2025. This is the thirteenth annual PADER for this product.

	INITIAL	FOLLOW-UP	TOTAL
15 Day Cases / 15 Day Reports	2	0	**2**
Serious Labeled Reports	0	0	**0**
Non-Serious Labeled Reports	0	0	**0**
Non-Serious Un-Labeled Reports	0	0	**0**
Total	**2**	**0**	**2**

5.3.6.1 NARRATIVE SUMMARY AND ANALYSIS

1. Number of 15-Day Alert Reports submitted during the reporting period: Two (2) reports were submitted during the reporting period.
2. Summary Tabulation of adverse events by body system: During the reporting period Avanthi, Inc. received two (2) expedited and zero (0) non-expedited initial reports and zero (0) follow up reports. These reports produced five (5) adverse event incidences spanning two (2) System Organ Classes (See Tabulation by System Organ Class (SOC) for All Events Reported).
3. Narrative discussion of 15-Day Alert Reports: Two (2) reports were received during the reporting period and is discussed below.

1. 20241100177:

This literature report was identified during the literature search performed on 25-Nov-2024. This case was reported by an other health care professional from Canada about a 70-year-old male who used Indomethacin and experienced Hypertensive Encephalopathy.

The patient's medical history included hypertension, gastroesophageal reflux disease and gout The patient presented to the emergency department (ED) with an episode of confusion lasting several hours. The Patient`s medications included trandolapril 4 mg orally once a day and pantoprazole 40 mg orally once a day. On an unknown date the patient started using Indomethacin 25 mg orally three times a day as needed for headache (Before 10 days of presentation to ED). The headache occurred daily in the context of poorly controlled blood pressure and was not associated with any other focal neurologic symptoms, infectious symptoms, or recent trauma. On the day of presentation, the patient was noted to be confused, disoriented, and unable to recall events of the prior week. At the time of arrival to the ED, he was hypertensive with a blood pressure of 190/110 mmHg and was disoriented to place, person, and time and the remainder of his neurological examination was normal with no focal neurologic deficits.

The patient laboratory investigations included Hemoglobin 151g/L, Leukocytes 5.7 billion per liter, Platelets 182 billion per liter, Sodium 138 mmol/L, Potassium 5 mmol/L, Chloride 102 mmol/L, Bicarbonate 28 mmol/L, Anion Gap 8 mmol/L, Calcium 2.25 mmol/L, Magnesium 0.84 mmol/L, Phosphate 1.18 mmol/L, Creatinine 114 micromole/Liter (changed to 95 μmol/L after isotonic intravenous fluids and discontinuation of NSAID and ACE inhibitor), liver enzymes AST 19 international unit per liter (U/L) and ALT 16 U/L and ALP 72 U/L, serum glucose 5.2 mmol/L, international normalized ratio (INR) 1.1, Prothrombin 12.3 seconds, cardiac markers Troponin I.-6 nanograms per liter (ng/L), Creatinine Kinase (CK) 133 U/L and thyroid stimulating hormone (TSH) 1.617 mIU/L. All the laboratory findings were within normal limits. Infectious workup including blood and urine cultures eventually returned negative. Computed tomography and magnetic resonance imaging of the brain, which were completed after the blood pressure was controlled, showed no acute process with no evidence of a stroke, bleed, or structural abnormality to explain his presentation. This workup effectively ruled out the alternative differential diagnoses that included metabolic, infectious or structural causes for his acute confusion.

The patient was admitted, the indomethacin was discontinued, and his hypertension was managed with amlodipine only, replacing the trandolapril. He was treated with amlodipine orally starting at 5 mg then titrated to effect to a total dose of 5 mg orally twice a day and then consolidated to

amlodipine 10 mg orally once a day. Specifically, management was per clinical practice guidelines, reducing mean arterial pressure (MAP) by no more than 25% within the first hour, and then targeting near 160/110 mmHg over the first 48 h, followed by titration to normal blood pressure targets thereafter. Once the blood pressure was controlled, the patient's confusion resolved and throughout hospitalization his headaches also began to improve as he remained normotensive. In follow-up several months later, his headaches resolved completely with continued blood pressure control. In light of his negative infectious, metabolic, and structural workup and with his improvement after drug discontinuation and blood pressure control, he was diagnosed with hypertensive encephalopathy triggered by indomethacin use. This diagnosis is further substantiated by the application of the Naranjo Adverse Drug Reaction Probability Scale where our patient's case scores a 6, indicating a probable adverse drug reaction. The patient was counseled to avoid NSAIDs in the future, including indomethacin, in particular because of his risk for blood pressure dysregulation. At the time of this report, outcome of the event was recovered.

According to the author the patient had transient episode of confusion with a manifestation of hypertensive encephalopathy triggered by indomethacin use. Hypertensive encephalopathy is a hypertensive emergency, and its pathophysiology is characterized by cerebral edema resulting from a sudden and severe increase in arterial pressure exceeding the capacity of neurovascular autoregulation.

Literature reference:

Plitman J, Raco V, Wu PE. Hypertensive Encephalopathy Triggered by Indomethacin Use. *Clin Case Rep.* 2024 Nov;12(11):e9604.

Case Comment:

The event of hypertensive encephalopathy in this 70-year-old male patient can be explained by the history of hypertension itself, hence the causality with the company drug is assessed as not related. The case was received from Canada where the Company does not have marketing authorization for the product.

2. 20250200022:

This literature report identified during the literature search on 17- Feb-2025. This case was reported by an other health care professional from Singapore regarding a preterm female Neonate (710 g weight) who experienced Necrotising enterocolitis (NEC), Pneumoperitoneum, Intestinal perforation and Ileo- ileal intussusception after administration of Indomethacin unspecified for patent ductus arteriosus (PDA).

The patient was delivered via emergency caesarean section from an in vitro fertilization dichorionic diamniotic twin pregnancy with premature prolonged rupture of membranes (PPROM) with a weight of 710 g and has no fetal abnormality. Two doses of antenatal dexamethasone were completed prior to delivery. The neonate was born pale, apnoeic and limp with an Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score of 6 at 1 minute and 7 at 5 minutes and was intubated at 8 minutes of life for poor respiratory effort and admitted to the neonatal intensive care unit (NICU) for mechanical ventilation. The patient was oxygenated for improvement of FiO2 45% to 21% with a single dose of surfactant at 38 minutes of life. Caffeine was started, and she was covered empirically with penicillin, gentamicin and fluconazole for presumed sepsis after PPROM until day 3 of life. She was started on central total parenteral nutrition (TPN) via an umbilical vein catheter from day 1 of life and managed to pass meconium on day 2 of life. Non-nutritive feeds were started on day 2 of life at 1 mL every 3 hours (11 mL/ kg/day) bolus feeding.

Postnatal echocardiogram on day 2 of life revealed a moderate 1.68mm patent ductus arteriosus (PDA) and she was treated with three doses of indomethacin from day 2 to day 4 of life with successful closure of the PDA. During the course of indomethacin, feeding was kept at 11 mL/kg/day. Initial gastric residuals were clear, but subsequently light brownish gastric residuals were noted on day 5 of life. Abdominal examination revealed a soft, non- distended abdomen with no erythema or palpable loops and abdominal radiograph showed distended bowel loops, worse on the right side, but no pneumoperitoneum. Feeds were held off for the rest of the day and gastric residuals returned to clear with gut rest. Bolus feeding was resumed on day 6 of life at 22 mL/kg/day (2ml every 3 hours). On day 7 of life, ventilatory support was removed and bolus feeding was increased to 34 mL/kg/day (3 mL every 3 hours) and thereafter, she developed two

episodes of regurgitation with associated apnoea then her feeding regime was changed to small, frequent feeds of 2 mL every 2 hours while persisting at 34 mL/kg/day and then her gastric residuals turned dark bilious, and she was kept nil by mouth for gut rest for next few days. On day 9 of life, the patient developed increased abdominal distension, persistent tachycardia and uncompensated metabolic acidosis and no haematochezia. Surgical consultation was sought and Arterial gas revealed a pH of 7.1, base excess of -14 and lactate of 9.6. The abdominal radiograph revealed pneumoperitoneum.

The clinical impression was spontaneous intestinal perforation because of indomethacin use and Differential diagnosis included NEC, as the patient was preterm and very low birth weight. Intestinal obstruction from other pathology such as intussusception was thought to be possible but less likely, as intussusception was rare in this age group. Urgent laparotomy was performed, which revealed feculent peritonitis from a large 1.5 cm perforation at the mid- ileum, 30 cm from the duodenal‑jejunal junction. About 10 cm distally, there was an ileo- ileal intussusception, which was 15 cm from the ileocecal junction. The proximal bowel appeared to have diffuse NEC with thin bowel walls. Multiple impending perforations were found: five distal and one proximal to the perforated site. The ileoileal intussusception was partially reduced and the remaining 3.5 cm of gangrenous intussuscepted bowel was resected. The intussusceptum is 40 cm from the duodenojejunal junction and the remaining small bowel post resection is 55 cm and full length of the colon remains intact. Bowel continuity was restored with an end- to- end ileo- ileal anastomosis. All serosal sites of impending perforation were reinforced with 6/0 polydioxanone sutures and the major proximal perforated site was exteriorised as a double barrel ileostomy. The abdomen was irrigated, and a Penrose drain was placed before abdominal closure.

Histopathology revealed an ischaemic patch as the lead point of intussusception. The edges of the full- thickness perforation also showed ischaemic changes and necrosis. Postoperative recovery was complicated by Acinetobacter baumannii and Enterobacter sakazakii bacteraemia, and a high stoma output of 72 mL/kg/ day. She was covered with intravenous antibiotics. A contrasted fluoroscopic study via the distal stoma showed no obstruction distally. She was kept nil by mouth for 10 days with TPN and subsequently tolerated escalation of Alfaré (extensively hydrolysed,

lactose- free, hypoallergenic) formula feeds. Stoma output came down drastically on Alfaré. The patient was started on distal stoma refeeding and is gaining weight. Other than her gastrointestinal issue, she had stable bilateral grade II intraventricular haemorrhage with no hydrocephalus and is managed conservatively with regular ultrasound monitoring. Subsequently, the stoma was closed, and she was discharged home on full oral feeds. At the time of this report, outcome of the event was recovered.

According to reporting author, this case was referred to the surgical team with pneumoperitoneum on day 9 of life, preceded by recurrent feed intolerance shortly after receiving indomethacin. Being physiologically stable, this was initially treated as ileus due to premature gut. Feeds were escalated, and antibiotics were started once pneumoperitoneum was detected. Preoperatively, the acute perforation was suspected to be SIP, given the risk factors of indomethacin exposure in a premature, very- low- birth- weight neonate with no prior signs of toxicity. The perforation occurred after the escalation of feeds in the second week of life, rather than the first few days of life. The persistent pattern of feed intolerance leading to intestinal perforation may hint towards intermittent obstruction, and early ultrasound abdomen by an experienced sonographer may have been able to pick up an intussusception prior to perforation. In this case the diagnosis of intussusception with NEC was made intraoperatively after the complication had occurred. The patient had mesenteric hypoperfusion from indomethacin use, forming an ischaemic functional lead point resulting in intussusception and ischaemic changes leading to NEC.

Literature reference:

Tu IWH, Chan EEH, Laksmi NK. Ileo-ileal intussusception and necrotising enterocolitis after indomethacin exposure masquerading clinically as solitary intestinal perforation. *BMJ Case Rep*. 2025 Jan 14;18(1):e263126.

Company comment:

This preterm female neonate had necrotising enterocolitis, pneumoperitoneum, intestinal perforation and ileo- ileal intussusception after administration of indomethacin for patent ductus arteriosus. According to the author, the patient had mesenteric hypoperfusion from indomethacin

use, forming an ischaemic functional lead point resulting in intussusception and ischaemic changes leading to necrotising enterocolitis, therefore, the causality with the drug is assessed as possible.

5.3.6.2 ACTIONS TAKEN DURING THIS REPORTING PERIOD DUE TO REPORTED ADVERSE DRUG EXPERIENCES

During the reporting period, no new studies with Indomethacin ER Capsules, USP 75 mg were initiated.

1. Safety labeling changes made during the reporting period: The version of Indomethacin ER Capsules, USP 75 mg (ANDA# 079175) US Prescribing Information has been updated from Rev. 08 to 09 (item ID # 6030/ 08 to 09) during the reporting period. The annotated version of the labeling documents with changes highlighted is provided in Appendix 3: Labelling changes during the reporting period. A copy of the current labeling document is included in Appendix 2: US Product Labelling.
2. Safety studies initiated: **None**
3. Summary of important foreign regulatory actions: **None**
4. Communications of new safety information: **None**
5. Marketing Authorization withdrawals or suspensions: **None**
6. Failure to obtain an extension of the current Marketing Authorization: **None**
7. Restrictions on the distribution of the medicinal product: **None**
8. Early termination or suspension of clinical trials: **None**

5.3.6.3 INDEX LINE LISTING

List of 15-Day Alert Reports by System Organ Class Submitted During Reporting Period

Total No. of Report(s)	Total Initial Report(s)	Total Follow-up Report(s)
2	**2**	**0**

Mfr. Control Number	Date(s) of Submission	Source/Event Verbatim (Preferred Terms)
System Organ Class: Gastrointestinal disorders		
20250200022	04-Mar-2025	*Literature* Necrotising enterocolitis [NECROTISING COLITIS] Intestinal perforation [INTESTINAL PERFORATION] Pneumoperitoneum [PNEUMOPERITONEUM] Ileo- ileal intussusception [INTUSSUSCEPTION]
System Organ Class: Nervous system disorders		
20241100177	09-Dec-2024	*Literature* Hypertensive Encephalopathy [HYPERTENSIVE ENCEPHALOPATHY]

List of Serious Listed Initial Reports

Total Initial Reports	Serious Listed Initial Reports
0	0

Mfr. Control Number	Source/Event Verbatim (Preferred Terms)	Drug Interaction
None Reported		

List of Non-Serious Unlisted Initial Reports

Total Initial Reports	Non-Serious Unlisted Initial Reports
0	0

Mfr. Control Number	Source/Event Verbatim (Preferred Terms)	Drug Interaction
None Reported		

List of Non-Serious Listed Initial Reports

Total Initial Reports	Non-Serious Listed Initial Reports
0	0

Mfr. Control Number	Source/Event Verbatim (Preferred Terms)	Drug Interaction
None Reported		

List of Serious Listed Follow-up Reports

Total Follow-up Reports	Serious Listed Follow-up Reports
0	0

Mfr. Control Number	Source/Event Verbatim (Preferred Terms)	Drug Interaction
None Reported		

List of Non-Serious Unlisted Follow-up Reports

Total Follow-up Reports	Non-Serious Unlisted Follow-up Reports
0	0

Mfr. Control Number	Source/Event Verbatim (Preferred Terms)	Drug Interaction
None Reported		

List of Non-Serious Listed Follow-up Reports

Total Follow-up Reports	Non-Serious Listed Follow-up Reports
0	0

Mfr. Control Number	Source/Event Verbatim (Preferred Terms)	Drug Interaction
None Reported		

Cases Sent as FDA 3500A Under Another (A)NDA

Mfr. Report No.	NDA No. Submit Date	Submission Mfr. Report No.	Event Verbatim [Preferred Terms]	Suspect Product(s)
None reported				

Tabulation by System Organ Class (SOC) for All Events Reported

System Organ Class (SOC) Preferred Term	Serious Unlisted	Serious Listed	Non-Serious Unlisted	Non-Serious Listed	Total Events	Total Cases
Gastrointestinal disorders	**4**	**0**	**0**	**0**	**4**	**1**
Intestinal perforation	1	0	0	0	1	1
Intussusception	1	0	0	0	1	1
Necrotising colitis	1	0	0	0	1	1
Pneumoperitoneum	1	0	0	0	1	1
Nervous system disorders	**1**	**0**	**0**	**0**	**1**	**1**
Hypertensive encephalopathy	1	0	0	0	1	1
Total	**5**	**0**	**0**	**0**	**5**	**2**

FDA 3500A (Non-Expedited Reports)

There were no non-expedited reports received during the reporting period.

Appendix 1: Index Line Listing

Report Name: Indomethacin ER Capsules, USP 75 mg_079175_PADER

Category: Annual Report

Agency Name: EVCTM
EVPM
FDA (Primary Agency)

Header

Company Name: Avanthi, Inc.
Approval: 79175
☐ Ingredient: INDOMETHACIN
☐ Trade Name: Indomethacin Extended-Release Capsules, USP
☐ Award Date: 2009/03/06 00:00:00
☒ Print all configuration criteria on separate cover pages (PDF Only)
☒ Print page numbers on report
☐ Allow access to report cases through Case Series

Licenses

Ingredient: INDOMETHACIN
Indication: (All Indications)
Formulation: (All Formulations)
Indomethacin Extended-Release Capsules, USP (US 79175)
Indomethacin Unspecified (US 79175)

Options(Applicable to non-15-Day Section only)

☒ Domestic Cases
☐ Foreign Cases
☒ Exclude Literature Cases
☒ Exclude Study Cases

Advanced Condition (None)

☐ Age Groups

☐ Elderly ☐ Neonate ☐ Foetus
☐ Infant ☐ Adolescent ☐ Adult
☐ Child

Date Range

Case Creation Date	Case Receipt Date		Case Locked/Archived Date
From	From	06-MAR-2024	From
To	To	05-MAR-2025	To

☒ Include Unlocked Cases ☐ Evaluate Primary Suspect Drug Only

☐ Add Cases not included in a previous reporting period Start Date

☒ Tab 1: FDA-3500A / VAERS Forms
☐ Suppress printing of non-serious listed reports ☒ Print FDA-3500A / VAERS Forms at the end
☒ Tab 2: Index of Submitted Forms in Tab 1
☒ Tab 3 Part 1: NDA Line Listing 15 Day Reports Submitted
☒ Tab 3 Part 2: Tabulation by System Organ Class of All Event Reports Submitted ☐ Group by Initial and Follow-up Case Event separately
☒ Tab 3 Part 3: Cases sent to FDA under another NDA
☒ Include Periodic Submissions

Start Page Number○○○1

Listing Options

○ List cases only once, under the primary event System Organ Class(SOC)
◉ List cases under all event System Organ Class(SOC)
☒ Include Index of Cases
☒ Include Summary of Cases Missing Assessments
☒ Include Summary of Unlocked Cases
☒ Include Listing of Nullified 15-day Alert Cases Submitted during the Reporting Period

☒ Use Periodic Numbering on the Reports

☒ Print MedWatch for Agency FDA for all Cases in the Report ☒ No Watermark

☐ Non 15 Day Cases ☒ 15 Day Submitted Cases ☐ Cases sent under another NDA

☐ Custom Case Summary Tabulation

Summary Report Title:

Advanced Condition: (None)

☐ Include these summary tabulations / listings based on the set of cases presented in the line listing

--None--

☐ Include these summary tabulations based on all cases

--None--

☐ Additional Separate Page Numbering for UD Summaries

☒ Case Count Summary Report

Index of Cases in Report

Company: **Avanthi, Inc.**
Approval: **79175**
Reporting Period: **06-Mar-2024 Through 05-Mar-2025**

Index of Cases in Report

Company: **Avanthi, Inc.**
Approval: **79175**
Reporting Period: **06-Mar-2024 Through 05-Mar-2025**

15 day Submission Cases

20241100177 20250200022

List of Serious Listed Initial Reports

Company:	**Avanthi, Inc.**
Approval:	**79175**
Reporting Period:	**06-Mar-2024 Through 05-Mar-2025**

Initial Reports **0** **Serious Listed Initial Reports** **0**

Page Number	Mfr. Control Number	Source / Event Verbatim [Preferred Terms]	Drug Interaction

NONE REPORTED

List of Non-Serious Unlisted Initial Reports

Company:	**Avanthi, Inc.**
Approval:	**79175**
Reporting Period:	**06-Mar-2024 Through 05-Mar-2025**

Initial Reports **0** **Non-Serious Unlisted Initial Reports** **0**

Page Number	Mfr. Control Number	Source / Event Verbatim [Preferred Terms]	Drug Interaction

NONE REPORTED

List of Non-Serious Listed Initial Reports

Company:	**Avanthi, Inc.**
Approval:	**79175**
Reporting Period:	**06-Mar-2024 Through 05-Mar-2025**

Initial Reports **0** **Non-Serious Listed Initial Reports** **0**

Page Number	Mfr. Control Number	Source / Event Verbatim [Preferred Terms]	Drug Interaction

NONE REPORTED

List of Serious Listed Follow-up Reports

Company: Avanthi, Inc.
Approval: 79175
Reporting Period: 06-Mar-2024 Through 05-Mar-2025
Followup Reports 0 **Serious Listed Followup Reports** 0

Page Number	Mfr. Control Number	Source / Event Verbatim [Preferred Terms]	Drug Interaction

NONE REPORTED

List of Non-Serious Unlisted Follow-up Reports

Company: Avanthi, Inc.
Approval: 79175
Reporting Period: 06-Mar-2024 Through 05-Mar-2025
Followup Reports 0 **Non-Serious Unlisted Followup Reports** 0

Page Number	Mfr. Control Number	Source / Event Verbatim [Preferred Terms]	Drug Interaction

NONE REPORTED

List of Non-Serious Listed Follow-up Reports

Company: Avanthi, Inc.
Approval: 79175
Reporting Period: 06-Mar-2024 Through 05-Mar-2025
Followup Reports 0 **Non-Serious Listed Followup Reports** 0

Page Number	Mfr. Control Number	Source / Event Verbatim [Preferred Terms]	Drug Interaction

NONE REPORTED

List of 15-Day Reports by System Organ Class
Submitted During Reporting Period

Company: **Avanthi, Inc.**
Approval: **79175**
Reporting Period: **06-Mar-2024 Through 05-Mar-2025**
Total Number of Reports: 2
Total Initial Reports: 2 (Domestic: 0 Foreign: 2) **Total Follow-up Reports: 0 (Domestic: 0 Foreign: 0)**

Mfr. Control Number	Date(s) of Submission	Source / Event Verbatim [Preferred Terms]
System Organ Class: Gastrointestinal disorders		
20250200022	04-Mar-2025	*Literature* Necrotising enterocolitis [NECROTISING COLITIS] Intestinal perforation [INTESTINAL PERFORATION] Pneumoperitoneum [PNEUMOPERITONEUM] Ileo- ileal intussusception [INTUSSUSCEPTION]
System Organ Class: Nervous system disorders		
20241100177	09-Dec-2024	*Literature* Hypertensive Encephalopathy [HYPERTENSIVE ENCEPHALOPATHY]

[1] Unlocked case [2] Follow-up case. [3] Downgraded Report

Listing of Nullified 15-Day Cases

Company: Avanthi, Inc.
Approval: 79175
Reporting Period: 06-Mar-2024 Through 05-Mar-2025
Reports 0

Mfr. Control Number	Submit Date	Nullification Date	Nullification Reason

NONE REPORTED

Tabulation by System Organ Class (SOC) for All Events Reported

Company: Avanthi, Inc.
Approval: 79175
Reporting Period: 06-Mar-2024 Through 05-Mar-2025

System Organ Class(SOC) Preferred Term	Serious Unlisted	Serious Listed	NonSerious Unlisted	NonSerious Listed	Total Events	Total Cases
Gastrointestinal disorders	4	0	0	0	4	1
Intestinal perforation	1	0	0	0	1	1
Intussusception	1	0	0	0	1	1
Necrotising colitis	1	0	0	0	1	1
Pneumoperitoneum	1	0	0	0	1	1
Nervous system disorders	1	0	0	0	1	1
Hypertensive encephalopathy	1	0	0	0	1	1
Total	5	0	0	0	5	2

Cases Sent As FDA 3500As Under Another NDA

Company: Avanthi, Inc.
Approval: 79175
Reporting Period: 06-Mar-2024 Through 05-Mar-2025

Mfr. Control No.	NDA No. Submit Date	Submission Mfr. Report No.	Event Verbatim [Preferred Terms]	Suspect Product(s)

NONE REPORTED

Cases Missing Assessment

No Cases Found

Cases Not Included in Report

No Cases Found

Index of Cases Not Locked in Report

No Cases Found

Case Count Summary Report

Company: **Avanthi, Inc.**
Approval: **79175**
Reporting Period: **06-Mar-2024 Through 05-Mar-2025**

	15 Day Cases	15 Day Reports	Serious Labeled Reports	Non Serious Labeled Reports	Non Serious UnLabeled Reports
INITIAL	2	2	0	0	0
FOLLOW-UP	0	0	0	0	0
TOTAL	**2**	**2**	**0**	**0**	**0**

Additional Expedited Report Forms

15 Day Submitted Cases

Mfr Report # 20241100177
UF/Importer Report #
FDA Use Only

A. PATIENT INFORMATION

1. **Patient Identifier** PRIVACY
In confidence

2. **Age at Time of Event:** 70 Years
or
Date of Birth: PRIVACY

3. **Sex** ☐ Female ☒ Male

4. **Weight** _____ lbs or _____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ **Adverse Event** and/or ☐ **Product Problem** (e.g., defects/malfunctions)

2. **Outcomes Attributed to Adverse Event** (Check all that apply)
☐ Death: _____ (mm/dd/yyyy)
☐ Life-threatening
☒ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☒ Other Serious (Important Medical Events)

3. **Date of Event** (mm/dd/yyyy)

4. **Date of This Report** (mm/dd/yyyy) 03/07/2025

5. **Describe Event or Problem**
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)
Hypertensive Encephalopathy [Hypertensive encephalopathy]

Case Description:
This literature report was identified during the literature search performed on 25-Nov-2024. This case was reported by an other health care professional from Canada about a 70-year-old male who used Indomethacin and experienced Hypertensive Encephalopathy.

The patient's medical history included hypertension, gastroesophageal reflux disease and gout The patient presented to the emergency department (ED) with an episode of confusion lasting several hours. The Patient`s medications included trandolapril 4 mg orally once a day and pantoprazole 40 mg orally once a day. On an unknown date the patient started
continued in additional info section...

6. **Relevant Tests/Laboratory Data, Including Dates**
Infectious workup including blood and urine cultures eventually returned negative.
Computed tomography and magnetic resonance imaging of the brain, which were completed after the blood pressure was controlled, showed no acute process with no evidence of a stroke, bleed, or structural abnormality
continued in additional info section...

7. **Other Relevant History, Including Preexisting Medical Conditions** (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
#1 Ongoing, Current Condition, Hypertension
#2 Current Condition, Gastrooesophageal reflux disease
#3 Current Condition, Gout
#4 Current Condition, Confusional state (lasting for several hours)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. **Name** (Give labeled strength & mfr/labeler)
#1. Indomethacin Unspecified (INDOMETHACIN) Unknown
#2.

2. **Dose, Frequency & Route Used**
#1. 25 milligram, tid (as(Continued)
#2.

3. **Therapy Dates** (if unknown, give duration) from/to (or best estimate)
#1.
#2.

4. **Diagnosis for Use** (Indication)
#1. Headache (Headache)
#2.

5. **Event Abated After Use Stopped or Dose Reduced?**
#1. ☐ Yes ☐ No ☒ Doesn't Apply
#2. ☐ Yes ☐ No ☐ Doesn't Apply

6. **Lot #**
#1.
#2.

7. **Exp. Date**
#1.
#2.

8. **Event Reappeared After Reintroduction?**
#1. ☐ Yes ☐ No ☒ Doesn't Apply
#2. ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC# or Unique ID**

10. **Concomitant Medical Products and Therapy Dates** (Exclude treatment of event)
1) Trandolapril (Trandolapril)
2) Pantoprazole (Pantoprazole)

G. ALL MANUFACTURERS

1. **Contact Office (and Manufacturing Site for Devices)**
Name: KVK-TECH, INC Anil Kumar Reddy
Address: 110 Terry Drive, Suite 200
Newtown, PA 18940 UNITED STATES

2. **Phone Number** +1 215-579-1842 1703

Email Address: ssyamala@kvktech.com

3. **Report Source** (Check all that apply)
☒ Foreign CAN
☐ Study
☒ Literature
☐ Consumer
☒ Health Professional
☐ User Facility
☐ Company Representative
☐ Distributor
☐ Other:

4. **Date Received by Manufacturer** (mm/dd/yyyy) 11/25/2024

5. (A)NDA # 79175
IND # _____
BLA # _____
PMA/510(k) # _____
Combination Product ☐ Yes
Pre-1938 ☐ Yes
OTC Product ☐ Yes

6. **If IND, Give Protocol #**

7. **Type of Report** (Check all that apply)
☐ 5-day ☐ 30-day
☐ 7-day ☒ Periodic
☐ 10-day ☐ Initial
☐ 15-day ☐ Follow-up # ___

9. **Manufacturer Report Number** 20241100177

8. **Adverse Event Term(s)** Hypertensive encephalopathy

E. INITIAL REPORTER

1. **Name and Address**
CANADA
Name and address withheld.

Phone # Withheld
Email Address Withheld

2. **Health Professional?** ☒ Yes ☐ No

3. **Occupation** Other Health Care Professional

4. **Initial Reporter Also Sent Report to FDA** ☐ Yes ☐ No ☒ Unk

MEDWATCH
3500A Facsimile *(continued)*

Mfr Report #	20241100177
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION

B5. EVENT DESCRIPTION (Continued)

using Indomethacin 25 mg orally three times a day as needed for headache (Before 10 days of presentation to ED). The headache occurred daily in the context of poorly controlled blood pressure and was not associated with any other focal neurologic symptoms, infectious symptoms, or recent trauma. On the day of presentation, the patient was noted to be confused, disoriented, and unable to recall events of the prior week. At the time of arrival to the ED, he was hypertensive with a blood pressure of 190/110 mmHg and was disoriented to place, person, and time and the remainder of his neurological examination was normal with no focal neurologic deficits.

The patient laboratory investigations included Hemoglobin 151g/L, Leukocytes 5.7 billion per liter, Platelets 182 billion per liter, Sodium 138 mmol/L, Potassium 5 mmol/L, Chloride 102 mmol/L, Bicarbonate 28 mmol/L, Anion Gap 8 mmol/L, Calcium 2.25 mmol/L, Magnesium 0.84 mmol/L, Phosphate 1.18 mmol/L, Creatinine 114 micromole/Liter (changed to 95 µmol/L after isotonic intravenous fluids and discontinuation of NSAID and ACE inhibitor), liver enzymes AST 19 international unit per liter (U/L) and ALT 16 U/L and ALP 72 U/L, serum glucose 5.2 mmol/L, international normalized ratio (INR) 1.1, Prothrombin 12.3 seconds, cardiac markers Troponin I.-6 nanograms per liter (ng/L), Creatinine Kinase (CK) 133 U/L and thyroid stimulating hormone (TSH) 1.617 mIU/L. All the laboratory findings were within normal limits. Infectious workup including blood and urine cultures eventually returned negative. Computed tomography and magnetic resonance imaging of the brain, which were completed after the blood pressure was controlled, showed no acute process with no evidence of a stroke, bleed, or structural abnormality to explain his presentation. This workup effectively ruled out the alternative differential diagnoses that included metabolic, infectious or structural causes for his acute confusion.

The patient was admitted, the indomethacin was discontinued, and his hypertension was managed with amlodipine only, replacing the trandolapril. He was treated with amlodipine orally starting at 5 mg then titrated to effect to a total dose of 5 mg orally twice a day and then consolidated to amlodipine 10 mg orally once a day. Specifically, management was per clinical practice guidelines, reducing mean arterial pressure (MAP) by no more than 25% within the first hour, and then targeting near 160/110 mmHg over the first 48 h, followed by titration to normal blood pressure targets thereafter. Once the blood pressure was controlled, the patient's confusion resolved and throughout hospitalization his headaches also began to improve as he remained normotensive. In follow-up several months later, his headaches resolved completely with continued blood pressure control. In light of his negative infectious, metabolic, and structural workup and with his improvement after drug discontinuation and blood pressure control, he was diagnosed with hypertensive encephalopathy triggered by indomethacin use. This diagnosis is further substantiated by the application of the Naranjo Adverse Drug Reaction Probability Scale where our patient's case scores a 6, indicating a probable adverse drug reaction. The patient was counseled to avoid NSAIDs in the future, including indomethacin, in particular because of his risk for blood pressure dysregulation.

At the time of this report, outcome of the event was recovered.

According to the author the patient had transient episode of confusion with a manifestation of hypertensive encephalopathy triggered by indomethacin use. Hypertensive encephalopathy is a hypertensive emergency, and its pathophysiology is characterized by cerebral edema resulting from a sudden and severe increase in arterial pressure exceeding the capacity of neurovascular autoregulation.

Literature reference:

Plitman J, Raco V, Wu PE. Hypertensive Encephalopathy Triggered by Indomethacin Use. Clin Case Rep. 2024 Nov;12(11):e9604.

Full text article attached.

Case Comment:
The event of hypertensive encephalopathy in this 70-year-old male patient can be explained by the history of hypertension itself, hence the causality with the company drug is assessed as not related.

B6. RELEVANT TESTS (Continued)

to explain his presentation.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Alanine aminotransferase	16 international unit per litre	40 7
2		Anion gap	8 millimole per litre	11 5
3		Aspartate aminotransferase	19 international unit per litre	40 7

4	Blood alkaline phosphatase	72 international unit per litre	150 40
5	Blood bicarbonate	28 millimole per litre	29 23
6	Blood calcium	2.25 millimole per litre	2.62 2.20
7	Blood chloride	102 millimole per litre	110 100
8	Blood creatine phosphokinase	133 international unit per litre	241
9	Blood creatinine 95 µmol/L after isotonic intravenous fluids and discontinuation of NSAID and ACE inhibitor	114 micromole per litre	110 64
10	Blood glucose	5.2 millimole per litre	7.7 3.8
11	Blood magnesium	0.84 millimole per litre	1.10 0.7
12	Blood phosphorus	1.18 millimole per litre	1.4 0.8
13	Blood potassium	5 millimole per litre	5 3.2
14	Blood pressure measurement At the time of arrival to the ED	190/110 millimetre of mercury	
15	Blood sodium	138 millimole per litre	145 135
16	Blood thyroid stimulating hormone	1.617 milli-international unit per litre	4.940 0.350
17	Haemoglobin	151 gram per litre	180 140
18	International normalised ratio	1.1	1.2 0.9
19	Mean arterial pressure no more than 25% within the first hour, and then targeting near 160/110 mmHg over the first 48 h,	not more than 25%	
20	Neurological examination	normal	
21	Platelet count	182 billion per litre	400 150
22	Prothrombin level	12.3 Second	14.1 9.9
23	Troponin I	6 nanogram per litre	27
24	White blood cell count	5.7 billion per litre	11 4

C2. DOSE, FREQUENCY & ROUTE USED (Continued)
Suspect Medication #1: 25 milligram, tid (as needed), Oral use

G3. Report source literature description

Journal: Clinical Case Reports
Author: Jane Plitman
Title: Hypertensive Encephalopathy Triggered by Indomethacin Use

MEDWATCH
3500A Facsimile *(continued)*

Mfr Report # 20241100177
UF/Importer Report #
FDA Use Only

Volume: 12(11) Year: 2024 Pages: e9604
Journal: Clinical Case Reports
Author: Vanessa Raco
Title: Hypertensive Encephalopathy Triggered by Indomethacin Use
Volume: 12(11) Year: 2024 Pages: e9604
Journal: Clinical Case Reports
Author: Peter E. Wu
Title: Hypertensive Encephalopathy Triggered by Indomethacin Use
Volume: 12(11) Year: 2024 Pages: e9604

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

3500A Facsimile

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting
KVK-Tech, Inc.

Oracle Corporation, FDA Facsimile Approval: 26-APR-2007

Mfr Report # 20250200022
UF/Importer Report #
FDA Use Only

A. PATIENT INFORMATION

1. **Patient Identifier** PRIVACY
In confidence

2. **Age at Time of Event:** or **Date of Birth:** PRIVACY

3. **Sex** ☒ Female ☐ Male

4. **Weight** 1.6 lbs or 0.7 kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ **Adverse Event** and/or ☐ **Product Problem** (e.g., defects/malfunctions)

2. **Outcomes Attributed to Adverse Event** (Check all that apply)
☐ Death: (mm/dd/yyyy)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☒ Other Serious (Important Medical Events)

3. **Date of Event** (mm/dd/yyyy)

4. **Date of This Report** (mm/dd/yyyy) 03/07/2025

5. **Describe Event or Problem**
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)
Necrotising enterocolitis [Necrotising colitis]
Intestinal perforation [Intestinal perforation]
Pneumoperitoneum [Pneumoperitoneum]
Ileo- ileal intussusception [Intussusception]

Case Description:
This literature report identified during the literature search on 17-Feb-2025. This case was reported by an other health care professional from Singapore regarding a preterm female Neonate (710 g weight) who experienced Necrotising enterocolitis (NEC), Pneumoperitoneum, Intestinal perforation and Ileo- ileal intussusception after administration of Indomethacin unspecified for patent ductus arteriosus (PDA).

The patient was delivered via emergency caesarean section from
continued in additional info section...

6. **Relevant Tests/Laboratory Data, Including Dates**
Oxygenation requirements improved from FiO2 45% to 21% with a single dose of surfactant at 38 minutes of life.
LABORATORY DATA
#1 Abdominal X-ray (Continued)
#2 Apgar score 6 , 1 min
#3 Apgar score 7 , 5 min
continued in additional info section...

7. **Other Relevant History, Including Preexisting Medical Conditions** (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
#1 Current Condition, Infantile apnoea
#2 Current Condition, Gait disturbance
#3 Current Condition, (Continued)
continued in additional info section...

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. **Name** (Give labeled strength & mfr/labeler)
#1. Indomethacin Unspecified (INDOMETHACIN) Unknown
#2.

2. **Dose, Frequency & Route Used**
#1. UNK, Unknown
#2.

3. **Therapy Dates** (if unknown, give duration) from/to (or best estimate)
#1. duration 3 days
#2.

4. **Diagnosis for Use** (Indication)
#1. patent ductus (Continued)
#2.

5. **Event Abated After Use Stopped or Dose Reduced?**
#1. ☐ Yes ☐ No ☒ Doesn't Apply
#2. ☐ Yes ☐ No ☐ Doesn't Apply

6. **Lot #**
#1.
#2.

7. **Exp. Date**
#1.
#2.

8. **Event Reappeared After Reintroduction?**
#1. ☐ Yes ☐ No ☒ Doesn't Apply
#2. ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC# or Unique ID**

10. **Concomitant Medical Products and Therapy Dates** (Exclude treatment of event)
1) Penicillin (Benzylpenicillin potassium)
2) Gentamicin (Gentamicin sulfate)
continued in additional info section...

G. ALL MANUFACTURERS

1. **Contact Office (and Manufacturing Site for Devices)**
Name
KVK-TECH, INC Anil Kumar Reddy
Address
110 Terry Drive, Suite 200
Newtown, PA 18940 UNITED STATES

2. **Phone Number**
+1 215-579-1842 1703

3. **Report Source** (Check all that apply)
☒ Foreign SGP
☐ Study
☒ Literature
☐ Consumer
☒ Health Professional
☐ User Facility
☐ Company Representative
☐ Distributor
☐ Other:

Email Address
ssyamala@kvktech.com

4. **Date Received by Manufacturer** (mm/dd/yyyy)
02/17/2025

5. (A)NDA # 79175
IND #
BLA #
PMA/ 510(k) #
Combination Product ☐ Yes
Pre-1938 ☐ Yes
OTC Product ☐ Yes

6. **If IND, Give Protocol #**

7. **Type of Report** (Check all that apply)
☐ 5-day ☐ 30-day
☐ 7-day ☒ Periodic
☐ 10-day ☐ Initial
☐ 15-day ☐ Follow-up #

9. **Manufacturer Report Number**
20250200022

8. **Adverse Event Term(s)**
Necrotising colitis, Intestinal perforation, Pneumoperitoneum, Intussusception

E. INITIAL REPORTER

1. **Name and Address**
SINGAPORE
Name and address withheld.

Phone #
Withheld

Email Address
Withheld

2. **Health Professional?** ☒ Yes ☐ No

3. **Occupation**
Other Health Care Professional

4. **Initial Reporter Also Sent Report to FDA** ☐ Yes ☐ No ☒ Unk

MEDWATCH
3500A Facsimile *(continued)*

Mfr Report #	20250200022
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION

B5. EVENT DESCRIPTION (Continued)

an in vitro fertilization dichorionic diamniotic twin pregnancy with premature prolonged rupture of membranes (PPROM) with a weight of 710 g and has no fetal abnormality. Two doses of antenatal dexamethasone were completed prior to delivery. The neonate was born pale, apnoeic and limp with an Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score of 6 at 1 minute and 7 at 5 minutes and was intubated at 8 minutes of life for poor respiratory effort and admitted to the neonatal intensive care unit (NICU) for mechanical ventilation. The patient was oxygenated for improvement of FiO2 45% to 21% with a single dose of surfactant at 38 minutes of life. Caffeine was started, and she was covered empirically with penicillin, gentamicin and fluconazole for presumed sepsis after PPROM until day 3 of life. She was started on central total parenteral nutrition (TPN) via an umbilical vein catheter from day 1 of life and managed to pass meconium on day 2 of life. Non- nutritive feeds were started on day 2 of life at 1 mL every 3 hours (11 mL/ kg/day) bolus feeding.

Postnatal echocardiogram on day 2 of life revealed a moderate 1.68mm patent ductus arteriosus (PDA) and she was treated with three doses of indomethacin from day 2 to day 4 of life with successful closure of the PDA. During the course of indomethacin, feeding was kept at 11 mL/kg/day. Initial gastric residuals were clear, but subsequently light brownish gastric residuals were noted on day 5 of life. Abdominal examination revealed a soft, non- distended abdomen with no erythema or palpable loops and abdominal radiograph showed distended bowel loops, worse on the right side, but no pneumoperitoneum. Feeds were held off for the rest of the day and gastric residuals returned to clear with gut rest. Bolus feeding was resumed on day 6 of life at 22 mL/kg/day (2ml every 3 hours). On day 7 of life, ventilatory support was removed and bolus feeding was increased to 34 mL/kg/day (3 mL every 3 hours) and thereafter, she developed two episodes of regurgitation with associated apnoea then her feeding regime was changed to small, frequent feeds of 2 mL every 2 hours while persisting at 34 mL/kg/day and then her gastric residuals turned dark bilious, and she was kept nil by mouth for gut rest for next few days. On day 9 of life, the patient developed increased abdominal distension, persistent tachycardia and uncompensated metabolic acidosis and no haematochezia. Surgical consultation was sought and Arterial gas revealed a pH of 7.1, base excess of -14 and lactate of 9.6. The abdominal radiograph revealed pneumoperitoneum.

The clinical impression was spontaneous intestinal perforation because of indomethacin use and Differential diagnosis included NEC, as the patient was preterm and very low birth weight. Intestinal obstruction from other pathology such as intussusception was thought to be possible but less likely, as intussusception was rare in this age group. Urgent laparotomy was performed, which revealed feculent peritonitis from a large 1.5 cm perforation at the mid- ileum, 30 cm from the duodenal–jejunal junction. About 10 cm distally, there was an ileo- ileal intussusception, which was 15 cm from the ileocecal junction. The proximal bowel appeared to have diffuse NEC with thin bowel walls. Multiple impending perforations were found: five distal and one proximal to the perforated site. The ileo- ileal intussusception was partially reduced and the remaining 3.5 cm of gangrenous intussuscepted bowel was resected. The intussusceptum is 40 cm from the duodenojejunal junction and the remaining small bowel post resection is 55 cm and full length of the colon remains intact. Bowel continuity was restored with an end- to- end ileo- ileal anastomosis. All serosal sites of impending perforation were reinforced with 6/0 polydioxanone sutures and the major proximal perforated site was exteriorised as a double barrel ileostomy. The abdomen was irrigated, and a Penrose drain was placed before abdominal closure.

Histopathology revealed an ischaemic patch as the lead point of intussusception. The edges of the full- thickness perforation also showed ischaemic changes and necrosis. Postoperative recovery was complicated by Acinetobacter baumannii and Enterobacter sakazakii bacteraemia, and a high stoma output of 72 mL/kg/ day. She was covered with intravenous antibiotics. A contrasted fluoroscopic study via the distal stoma showed no obstruction distally. She was kept nil by mouth for 10 days with TPN and subsequently tolerated escalation of Alfaré (extensively hydrolysed, lactose- free, hypoallergenic) formula feeds. Stoma output came down drastically on Alfaré. The patient was started on distal stoma refeeding and is gaining weight. Other than her gastrointestinal issue, she had stable bilateral grade II intraventricular haemorrhage with no hydrocephalus and is managed conservatively with regular ultrasound monitoring. Subsequently, the stoma was closed, and she was discharged home on full oral feeds.

At the time of this report, outcome of the event was recovered.

According to reporting author, this case was referred to the surgical team with pneumoperitoneum on day 9 of life, preceded by recurrent feed intolerance shortly after receiving indomethacin. Being physiologically stable, this was initially treated as ileus due to premature gut. Feeds were escalated, and antibiotics were started once pneumoperitoneum was detected. Preoperatively, the acute perforation was suspected to be SIP, given the risk factors of indomethacin exposure in a premature, very- low- birth- weight neonate with no prior signs of toxicity. The perforation occurred after the escalation of feeds in the second week of life, rather than the first few days of life. The persistent pattern of feed intolerance leading to intestinal perforation may hint towards intermittent obstruction, and early ultrasound abdomen by an experienced sonographer may have been able to pick up an intussusception prior to perforation. In this case the diagnosis of intussusception with NEC was made intraoperatively after the complication had occurred. The patient had mesenteric hypoperfusion from indomethacin use, forming an ischaemic functional lead point resulting in intussusception and ischaemic changes leading to NEC.

Literature reference:

Mfr Report # 20250200022
UF/Importer Report #
FDA Use Only

Tu IWH, Chan EEH, Laksmi NK. Ileo-ileal intussusception and necrotising enterocolitis after indomethacin exposure masquerading clinically as solitary intestinal perforation. BMJ Case Rep. 2025 Jan 14;18(1):e263126.

Full text article attached.

Case Comment:
This preterm female neonate had necrotising enterocolitis, pneumoperitoneum, intestinal perforation and ileo- ileal intussusception after administration of indomethacin for patent ductus arteriosus. According to the author, the patient had mesenteric hypoperfusion from indomethacin use, forming an ischaemic functional lead point resulting in intussusception and ischaemic changes leading to necrotising enterocolitis, therefore, the causality with the drug is assessed as possible.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Abdominal X-ray showed distended bowel loops, worse on the right side, but no pneumoperitoneum		
4		Base excess	-14	
5		Blood gases revealed a pH of 7.1		
6		Blood lactic acid	9.6	
7		Echocardiogram Day 2-moderate 1.68mm patent ductus arteriosus (PDA)		
8		Laparotomy feculent peritonitis from a large 1.5 cm perforation at the mid- ileum, 30 cm from the duodenal–jejunal junction		
9		Physical examination soft, non- distended abdomen with no erythema or palpable loops.		
10		Physical examination revealed pneumoperitoneum		

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
3		Current Condition Endotracheal intubation	She was intubated at 8 minutes of life for poor respiratory effort
4		Current Condition Mechanical ventilation	admitted to the neonatal intensive care unit (NICU) for mechanical ventilation
5		Current Condition Parenteral nutrition	She was started on central total parenteral nutrition (TPN) via an umbilical vein catheter from day 1 of life and managed to pass meconium on day 2 of life
6		Current Condition Patent ductus arteriosus	
7		Current Condition Apnoea	

Mfr Report # 20250200022
UF/Importer Report #
FDA Use Only

8	Current Condition Regurgitation	
9	Current Condition Abdominal distension	
10	Current Condition Tachycardia	
11	Current Condition Metabolic acidosis	
12	Current Condition Intraventricular haemorrhage neonatal	Bilateral and was stable

C4. DIAGNOSIS FOR USE (Continued)
#1:patent ductus arteriosus (Patent ductus arteriosus)

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

3) Fluconazole (Fluconazole)

G3. Report source literature description

Journal: BMJ Case Rep.
Author: Irene Wen Hui Tu
Title: Ileo-ileal intussusception and necrotising enterocolitis after indomethacin exposure masquerading clinically as solitary intestinal perforation
Volume: 18(1) Year: 2025 Pages: e263126
Journal: BMJ Case Rep.
Author: Esther Ern Hwei Chan
Title: Ileo-ileal intussusception and necrotising enterocolitis after indomethacin exposure masquerading clinically as solitary intestinal perforation
Volume: 18(1) Year: 2025 Pages: e263126
Journal: BMJ Case Rep.
Author: Narasimhan Kannan Laksmi
Title: Ileo-ileal intussusception and necrotising enterocolitis after indomethacin exposure masquerading clinically as solitary intestinal perforation
Volume: 18(1) Year: 2025 Pages: e263126

Appendix 2: US Product Labelling

INDOMETHACIN EXTENDED-RELEASE CAPSULES USP

Rx Only

Item ID# 006030/09

603009

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INDOMETHACIN EXTENDED-RELEASE CAPSULES USP 75 mg safely and effectively. See full prescribing information for INDOMETHACIN EXTENDED-RELEASE CAPSULES.

INDOMETHACIN extended-release capsules for oral use
Initial U.S. Approval: 1965

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions (5.9)	07/2024
Adverse Reactions (6.2)	07/2024

---------- INDICATIONS AND USAGE ----------

Indomethacin extended-release capsules are a nonsteroidal anti-inflammatory drug indicated for:

- Moderate to severe rheumatoid arthritis including acute flares of chronic disease
- Moderate to severe ankylosing spondylitis
- Moderate to severe osteoarthritis
- Acute painful shoulder (bursitis and/or tendinitis) (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)
- The dosage for moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis is one indomethacin extended-release 75 mg capsule daily (2.2)
- The dosage for acute painful shoulder (bursitis and/or tendinitis) is one indomethacin extended-release 75 mg capsule once or twice daily (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Indomethacin extended-release capsules: 75 mg (3)

---------- CONTRAINDICATIONS ----------

- Known hypersensitivity to indomethacin or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of indomethacin extended-release capsules in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of indomethacin extended-release capsules in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: Indomethacin extended-release capsules are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue indomethacin extended-release capsules at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including indomethacin extended-release capsules, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1).
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥ 3%) are headache, dizziness, dyspepsia and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact KVK-Tech, Inc. at 1-800-862-3895 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking indomethacin extended-release capsules with drugs that interfere with hemostasis. Concomitant use of indomethacin extended-release capsules and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with indomethacin extended-release capsules may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with indomethacin extended-release capsules in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with indomethacin extended-release capsules can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

---------- USE IN SPECIFIC POPULATIONS ----------

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of indomethacin extended-release capsules in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised 07/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].**
- **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

Indomethacin extended-release capsules are indicated for:

- Moderate to severe rheumatoid arthritis including acute flares of chronic disease
- Moderate to severe ankylosing spondylitis
- Moderate to severe osteoarthritis
- Acute painful shoulder (bursitis and/or tendinitis)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of indomethacin extended-release capsules and other treatment options before deciding to use indomethacin extended-release capsules. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

After observing the response to initial therapy with indomethacin, the dose and frequency should be adjusted to suit an individual patient's needs.

Adverse reactions generally appear to correlate with the dose of indomethacin. Therefore, every effort should be made to determine the lowest effective dosage for the individual patient.

THIS SECTION PREDOMINANTLY REFERENCES THE INDOMETHACIN IMMEDIATE-RELEASE CAPSULE ORAL DOSAGE AND IS INTENDED TO PROVIDE GUIDANCE IN USING INDOMETHACIN EXTENDED-RELEASE CAPSULES, 75 MG

Indomethacin extended-release capsules, 75 mg once a day can be substituted for indomethacin immediate-release capsules, 25 mg three times a day. However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours [*see Clinical Pharmacology (12)*]. In addition, Indomethacin extended-release capsules, 75 mg twice a day can be substituted for indomethacin immediate-release capsules, USP 50 mg three times a day.

Indomethacin extended-release capsules may be substituted for all the indications for indomethacin immediate-release capsules, USP except acute gouty arthritis.

Dosage Recommendations for Active Stages of the Following:

2.2 Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis

Indomethacin immediate-release capsules, 25 mg twice a day or three times a day. If this is well tolerated, increase the daily dosage by 25 mg or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150 - 200 mg is reached. Doses above this amount generally do not increase the effectiveness of the drug.

In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and observe the patient closely.

If severe adverse reactions occur, stop the drug. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, indomethacin extended-release capsules should be used with greater care in the elderly [*see Use in Specific Populations (8.5)*].

2.3 Acute painful shoulder (bursitis and/or tendinitis)

Indomethacin immediate-release capsules 75-150 mg daily in 3 or 4 divided doses.

Discontinue indomethacin extended-release capsules treatment after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.

3 DOSAGE FORMS AND STRENGTHS

Indomethacin Extended-release Capsules USP 75 mg - yellow opaque cap, natural body with black imprint "K 16" on both cap and body, filled with white pellets.

4 CONTRAINDICATIONS

Indomethacin extended-release capsules are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as indomethacin, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of indomethacin extended-release capsules in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If indomethacin extended-release capsules are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including indomethacin, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue indomethacin extended-release capsules until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including indomethacin.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue indomethacin extended-release capsules immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including indomethacin extended-release capsules, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of indomethacin may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of indomethacin extended-release capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If indomethacin extended-release capsules are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of indomethacin extended-release capsules in patients with advanced renal disease. The renal effects of indomethacin extended-release capsules may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating indomethacin extended-release capsules. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of indomethacin extended-release capsules [*see Drug Interactions (7)*]. Avoid the use of indomethacin extended-release capsules in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If indomethacin extended-release capsules are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

It has been reported that the addition of the potassium-sparing diuretic, triamterene, to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Both Indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.

5.7 Anaphylactic Reactions

Indomethacin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to indomethacin and in patients with aspirin-sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, indomethacin extended-release capsules are contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When indomethacin extended-release capsules are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including indomethacin, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of indomethacin extended-release capsules at the first appearance of skin rash or any other sign of hypersensitivity. Indomethacin extended-release capsules are contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as indomethacin extended-release capsules. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue indomethacin extended-release capsules and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including indomethacin extended-release capsules, in pregnant women at about 30 weeks gestation and later. NSAIDs, including indomethacin extended-release capsules, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including indomethacin extended-release capsules, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit indomethacin extended-release capsules use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if indomethacin extended-release capsules treatment extends beyond 48 hours. Discontinue indomethacin extended-release capsules if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

5.12 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with indomethacin extended-release capsules has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including indomethacin extended-release capsules, may increase the risk of bleeding events. Co-morbid conditions, such as coagulation disorders, or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.13 Masking of Inflammation and Fever

The pharmacological activity of indomethacin extended-release capsules in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

5.15 Central Nervous System Effects

Indomethacin extended-release capsules may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. Discontinue indomethacin extended-release capsules if severe CNS adverse reactions develop.

Indomethacin extended-release capsules may cause drowsiness; therefore, caution patients about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin extended-release capsules.

5.16 Ocular Effects

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin extended-release capsules. Be alert to the possible association between the changes noted and indomethacin extended-release capsules. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. Indomethacin extended-release capsules are not indicated for long-term treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.12)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving indomethacin immediate-release capsules than in the group taking indomethacin suppositories or placebo.

In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with indomethacin immediate-release capsules or suppositories was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

The adverse reactions for indomethacin immediate-release capsules listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

The adverse reactions reported with indomethacin immediate-release capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the capsules.

Table 1 Summary of Adverse Reactions for Indomethacin Capsules

Incidence greater than 1%	***Incidence less than 1%***	
GASTROINTESTINAL		
nausea* with or without vomiting dyspepsia* (including indigestion, heartburn and epigastric pain) diarrhea abdominal distress or pain constipation	anorexia bloating (includes distension) flatulence peptic ulcer gastroenteritis rectal bleeding proctitis single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines intestinal ulceration associated with stenosis and obstruction	gastrointestinal bleeding without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis ulcerative stomatitis toxic hepatitis and jaundice (some fatal cases have been reported) intestinal strictures (diaphragms) pancreatitis
CENTRAL NERVOUS SYSTEM		
headache (11.7%) dizziness* vertigo somnolence depression and fatigue (including malaise and listlessness)	anxiety (includes nervousness) muscle weakness involuntary muscle movements insomnia muzziness psychic disturbances including psychotic episodes mental confusion drowsiness	light-headedness syncope paresthesia aggravation of epilepsy and parkinsonism depersonalization coma peripheral neuropathy convulsion dysarthria
SPECIAL SENSES		
tinnitus	ocular - corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin	blurred vision diplopia hearing disturbances, deafness
CARDIOVASCULAR		
None	hypertension hypotension tachycardia chest pain	congestive heart failure arrhythmia; palpitations
METABOLIC		
None	edema weight gain fluid retention flushing or sweating	hyperglycemia glycosuria hyperkalemia
INTEGUMENTARY		
none	pruritus rash; urticaria petechiae or ecchymosis	exfoliative dermatitis erythema nodosum loss of hair Stevens-Johnson syndrome erythema multiforme toxic epidermal necrolysis
HEMATOLOGIC		
None	leukopenia bone marrow depression anemia secondary to obvious or occult gastrointestinal bleeding	aplastic anemia hemolytic anemia agranulocytosis thrombocytopenic purpura disseminated intravascular coagulation
HYPERSENSITIVITY		
None	acute anaphylaxis acute respiratory distress rapid fall in blood pressure resembling a shock-like state angioedema	dyspnea asthma purpura angiitis pulmonary edema fever
GENITOURINARY		
None	hematuria vaginal bleeding proteinuria nephrotic syndrome interstitial nephritis	BUN elevation renal insufficiency, including renal failure
MISCELLANEOUS		
None	epistaxis breast changes, including enlargement and tenderness, or gynecomastia	

* Reactions occurring in 3% to 9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked.)

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed**.**

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

19.5"

15"

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured by:
KVK-TECH INC.
110 Terry Drive
Newtown, PA 18940

For more information, go to www.kvktech.com or call our customer service at 1-800-862-3895

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued or Revised: July 2024

Causal relationship unknown: Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

Cardiovascular: Thrombophlebitis

Hematologic: Although there have been several reports of leukemia, the supporting information is weak

Genitourinary: Urinary frequency
A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A(-) hemolytic streptococcus, has been described in persons treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of indomethacin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Appendages: Exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE).

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with indomethacin.

Table 2 Clinically Significant Drug Interactions with Indomethacin

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of indomethacin extended-release capsules with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.12)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of indomethacin extended-release capsules and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.12)*]. Indomethacin extended-release capsules is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of indomethacin extended-release capsules and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of indomethacin extended-release capsules and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. It has been reported that the addition of triamterene to a maintenance schedule of indomethacin extended-release capsules resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin extended-release capsules and triamterene should not be administered together. Both indomethacin extended-release capsules and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin extended-release capsules and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.
Intervention:	Indomethacin and triamterene should not be administered together. During concomitant use of indomethacin extended-release capsules with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. Be aware that indomethacin and potassium-sparing diuretics may both be associated with increased serum potassium levels [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of indomethacin extended-release capsules and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of indomethacin extended-release capsules and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of indomethacin extended-release capsules and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of indomethacin extended-release capsules and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of indomethacin extended-release capsules and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of indomethacin with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*]. Combined use with diflunisal may be particularly hazardous because diflunisal causes significantly higher plasma levels of indomethacin [*see Clinical Pharmacology (12.3)*]. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage.
Intervention:	The concomitant use of indomethacin with other NSAIDs or salicylates, especially diflunisal, is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of indomethacin extended-release capsules and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of indomethacin extended-release capsules and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Probenecid	
Clinical Impact:	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.
Intervention:	During the concomitant use of indomethacin extended-release capsules and probenecid, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.

Effects on Laboratory Tests

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including indomethacin extended-release capsules, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of indomethacin extended-release capsules use between about 20 and 30 weeks of gestation, and avoid indomethacin extended-release capsules use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including indomethacin extended-release capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies retarded fetal ossification was observed with administration of indomethacin to mice and rats during organogenesis at doses 0.1 and 0.2 times, respectively, the maximum recommended human dose (MRHD, 200 mg). In published studies in pregnant mice, indomethacin produced maternal toxicity and death, increased fetal resorptions, and fetal malformations at 0.1 times the MRHD. When rat and mice dams were dosed during the last three days of gestation, indomethacin produced neuronal necrosis in the offspring at 0.1 and 0.05 times the MRHD, respectively [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as indomethacin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including indomethacin extended-release capsules, can cause premature closure of the fetal ductus arteriosus (see Data).

Oligohydramnios/Neonatal Renal Impairment

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If indomethacin extended-release capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue indomethacin extended-release capsules and follow up according to clinical practice (see Data).

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal data

Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.1 times [mice] and 0.2 times [rats] the MRHD on a mg/m2 basis, respectively) considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.1 to 0.4 times MRHD on a mg/m2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations.

In rats and mice, maternal indomethacin administration of 4.0 mg/kg/day (0.2 times and 0.1 times the MRHD on a mg/m2 basis) during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups (0.1 times and 0.05 times the MRHD on a mg/m2 basis). Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.

8.2 Lactation

Risk Summary

Based on available published clinical data, indomethacin may be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for indomethacin extended-release capsules and any potential adverse effects on the breastfed infant from the indomethacin extended-release capsules or from the underlying maternal condition.

Data

In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% of the maternal weight- adjusted dose. In another study indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The estimated infant dose of indomethacin from breast milk was less than 30 mcg/day or 4.5 mcg/ kg/day assuming breast milk intake of 150 mL/kg/day.

This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of patent ductus arteriosus.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including indomethacin extended-release capsules, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including indomethacin extended-release capsules, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients 14 years of age and younger has not been established.

Indomethacin extended-release capsules should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk.

In experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with indomethacin immediate-release capsules, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of indomethacin immediate-release capsules.

If a decision is made to use indomethacin for pediatric patients two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities. If indomethacin treatment is instituted, a suggested starting dose is 1-2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 3 mg/kg/day or 150-200 mg/day, whichever is less. Limited data are available to support the use of a maximum daily dosage of 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)*].

Indomethacin may cause confusion or rarely, psychosis [*see Adverse Reactions (6.1)*]; physicians should remain alert to the possibility of such adverse effects in the elderly.

Indomethacin and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use caution in this patient population, and it may be useful to monitor renal function [*see Clinical Pharmacology (12.3)*]

10 OVERDOSAGE

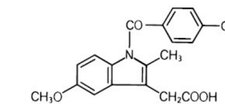
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

Indomethacin extended-release capsules are nonsteroidal anti-inflammatory drugs, available as capsules containing 75 mg of indomethacin, administered for oral use. The chemical name is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The molecular weight is 357.8. Its molecular formula is $C_{19}H_{16}ClNO_4$, and it has the following chemical structure.



Indomethacin is a pale yellow to yellow-tan crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali.

The inactive ingredients in Indomethacin Extended-Release Capsules, 75 mg include: corn starch, D&C Yellow # 10, gelatin, mannitol, povidone, sucrose, talc, and titanium dioxide.

This product meets USP Drug Release Test 2 Specifications.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Indomethacin has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of indomethacin extended-release capsules, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Indomethacin is a potent inhibitor of prostaglandin synthesis in vitro. Indomethacin concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

Absorption

Following single oral doses of indomethacin immediate-release capsules 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin immediate-release capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of indomethacin oral suspension was found to be bioequivalent to a 50 mg indomethacin capsule when each was administered with food. With a typical therapeutic regimen of 25 or 50 mg three times a day, the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

Indomethacin extended-release capsules 75 mg are designed to release 25 mg of the drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24-hour period, the cumulative amount and time-course of indomethacin absorption from a single indomethacin extended-release capsule are comparable to those of 3 doses of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals.

Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin immediate-release capsules 25 mg given at 0, 6 and 12 hours daily. However, there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.

Distribution

Indomethacin is highly bound to protein in plasma (about 99%) over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta, and appears in breast milk.

Elimination

Metabolism

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of each metabolite and of indomethacin are formed.

Excretion

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 60% of an oral dose is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin). The mean half-life of indomethacin is estimated to be about 4.5 hours.

Specific Populations

Pediatric: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in patients with hepatic impairment.

Renal Impairment: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in patients with renal impairment [*see Warnings and Precautions (5.6)*].

Drug Interaction Studies

Aspirin:

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20% [*see Drug Interactions (7)*].

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

Diflunisal:

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.05 times the MRHD on a mg/m2 basis), indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73 to 110 weeks) and the mouse (dosing period 62 to 88 weeks) at doses up to 1.5 mg/kg/day (0.04 times [mice] and 0.07 times [rats] the MRHD on a mg/m2 basis, respectively).

Mutagenesis

Indomethacin did not have any mutagenic effect in in vitro bacterial tests and a series of in vivo tests including the host-mediated assay, sex-linked recessive lethals in Drosophila, and the micronucleus test in mice.

Impairment of Fertility

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.01 times the MRHD on a mg/m2 basis) or a two litter reproduction study in rats (0.02 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

Indomethacin extended-release capsules affords relief of symptoms; it does not alter the progressive course of the underlying disease.

Indomethacin extended-release capsules suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength. Indomethacin extended-release capsules may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

16 HOW SUPPLIED/STORAGE AND HANDLING

Indomethacin extended-release capsules, 75 mg each, are supplied as yellow opaque cap and natural body with black imprint "K 16" on both cap and body, filled with white pellets.

Bottles of 30 capsules, NDC 10702-016-03

Bottles of 60 capsules, NDC 10702-016-06

Bottles of 90 capsules, NDC 10702-016-09

Bottles of 100 capsules, NDC 10702-016-01

Bottles of 500 capsules, NDC 10702-016-50

Bottles of 1000 capsules, NDC 10702-016-10

Storage

Store at room temperature 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with indomethacin extended-release capsules and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop indomethacin extended-release capsules and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions, including DRESS

Advise patients to stop taking indomethacin extended-release capsules immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10)*].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including indomethacin extended-release capsules, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity

Inform pregnant women to avoid use of indomethacin extended-release capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with indomethacin extended-release capsules is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of indomethacin extended-release capsules with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with indomethacin until they talk to their healthcare provider [*see Drug Interactions (7)*].

Manufactured by:
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KVK | TECH

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Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

  NSAIDs should only be used:
  - exactly as prescribed
  - at the lowest dose possible for your treatment
  - for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured by:
KVK-TECH INC.
110 Terry Drive
Newtown, PA 18940

For more information, go to www.kvktech.com or call our customer service at 1-800-862-3895

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued or Revised: July 2024

Appendix 3: Labelling changes during the reporting period

Side by Side Comparison

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
HIGHLIGHTS OF PRESCRIBING INFORMATION	**HIGHLIGHTS OF PRESCRIBING INFORMATION**		**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use INDOCIN® SR safely and effectively. See full prescribing information for INDOCIN SR.	**These highlights do not include all the information needed to use INDOMETHACIN EXTENDED-RELEASE CAPSULES USP 75 mg safely and effectively. See full prescribing information for INDOMETHACIN EXTENDED-RELEASE CAPSULES.**		**These highlights do not include all the information needed to use INDOMETHACIN EXTENDED-RELEASE CAPSULES USP 75 mg safely and effectively. See full prescribing information for INDOMETHACIN EXTENDED-RELEASE CAPSULES.**
INDOCIN SR (indomethacin) extended-release capsules for oral use Initial U.S. Approval: 1965 **WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS** ***See full prescribing information for complete boxed warning.*** • **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)** • **INDOCIN SR is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**	**Indomethacin extended-release capsules for oral use Initial U.S. Approval: 1965** **WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS** ***See full prescribing information for complete boxed warning.*** • **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**		**Indomethacin extended-release capsules for oral use Initial U.S. Approval: 1965** **WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS** ***See full prescribing information for complete boxed warning.*** • **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
• **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**	• **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)** • **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**		• **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)** • **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**
----------RECENT MAJOR CHANGES-------- Warnings and Precautions, Drug Reaction with Eosinophilia and Systemic Symptoms (5.10) 04/2021 Warnings and Precautions, Fetal Toxicity (5.11) 04/2021		1	**----------RECENT MAJOR CHANGES----------** Warnings and Precauctions (5.9) 07/2024 Adverse Reactions (6.2) 07/2024
----------INDICATIONSANDUSAGE---------- INDOCIN SR is a nonsteroidal anti-inflammatory drug indicated for: • Moderate to severe rheumatoid arthritis including acute flares of chronic disease • Moderate to severe ankylosing spondylitis • Moderate to severe osteoarthritis • Acute painful shoulder (bursitis and/or tendinitis) (1)	**--------INDICATIONS AND USAGE --------** Indomethacin extended-release capsules are a nonsteroidal anti-inflammatory drug indicated for: • Moderate to severe rheumatoid arthritis including acute flares of chronic disease • Moderate to severe ankylosing spondylitis		**----------INDICATIONS AND USAGE ----------** Indomethacin extended-release capsules are a nonsteroidal anti-inflammatory drug indicated for: • Moderate to severe rheumatoid arthritis including acute flares of chronic disease • Moderate to severe ankylosing spondylitis • Moderate to severe osteoarthritis

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
	• Moderate to severe osteoarthritis • Acute painful shoulder (bursitis and/or tendinitis) (1)		Acute painful shoulder (bursitis and/or tendinitis) (1)
---------DOSAGE AND ADMINISTRATION---- • Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1) • The dosage for moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis is one INDOCIN SR 75 mg capsule daily (2.2) • The dosage for acute painful shoulder (bursitis and/or tendinitis) is one INDOCIN SR 75 mg capsule once or twice daily (2.3)	**---DOSAGE AND ADMINISTRATION--** • Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1) • The dosage for moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis is one indomethacin extended-release 75 mg capsule daily (2.2) • The dosage for acute painful shoulder (bursitis and/or tendinitis) is one indomethacin extended-release 75 mg capsule once or twice daily (2.3)		**------DOSAGE AND ADMINISTRATION-----** • Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1) • The dosage for moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis is one indomethacin extended-release 75 mg capsule daily (2.2) • The dosage for acute painful shoulder (bursitis and/or tendinitis) is one indomethacin extended-release 75 mg capsule once or twice daily (2.3)
-----DOSAGE FORMS AND STRENGTHS------ INDOCIN SR (indomethacin) extended-release capsules: 75 mg (3)	**--DOSAGE FORMS AND STRENGTHS-** Indomethacin extended-release capsules: 75 mg (3)		**----- DOSAGE FORMS AND STRENGTHS ----** Indomethacin extended-release capsules: 75 mg (3)
----------CONTRAINDICATIONS----------	**---------CONTRAINDICATIONS----------** • Known hypersensitivity to indomethacin or any components of the drug product (4)		**---------- CONTRAINDICATIONS ----------** • Known hypersensitivity to methylphenidate or product components (4).

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
• Known hypersensitivity to indomethacin or any components of the drug product (4) • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4) • In the setting of CABG surgery (4)	• History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4) • In the setting of CABG surgery (4)		Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4).
-------WARNINGS AND PRECAUTIONS------ • Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3) • Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7) • Heart Failure and Edema: Avoid use of INDOCIN SR in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5) • Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of INDOCIN SR in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)	**----WARNINGS AND PRECAUTIONS---** • Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3) • Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7) • Heart Failure and Edema: Avoid use of indomethacin extended-release capsules in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5) • Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of indomethacin extended-release capsules in patients with advanced renal disease unless benefits are expected to		**-------WARNINGS AND PRECAUTIONS------** • Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3) • Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7) • Heart Failure and Edema: Avoid use of indomethacin extended-release capsules in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5) • Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of indomethacin extended-release capsules in patients with advanced renal disease unless benefits are expected to outweigh risk of

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
• Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7) • Exacerbation of Asthma Related to Aspirin Sensitivity: INDOCIN SR is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8) • Serious Skin Reactions: Discontinue INDOCIN SR at first appearance of skin rash or other signs of hypersensitivity (5.9) • Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10) • Fetal Toxicity: Limit use of NSAIDs, including INDOCIN SR, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1) • Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)	outweigh risk of worsening renal function (5.6) • Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7) • Exacerbation of Asthma Related to Aspirin Sensitivity: Indomethacin extended-release capsules are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8) • Serious Skin Reactions: Discontinue indomethacin extended-release capsules at first appearance of skin rash or other signs of hypersensitivity (5.9) • Drug Rection with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10) • Fetal Toxicity: Limit use of NSAIDs, including indomethacin extended-release capsules, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1). • Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)		worsening renal function (5.6) • Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7) • Exacerbation of Asthma Related to Aspirin Sensitivity: Indomethacin extended-release capsules are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8) • Serious Skin Reactions: Discontinue indomethacin extended-release capsules at first appearance of skin rash or other signs of hypersensitivity (5.9) • Drug Rection with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10) • Fetal Toxicity: Limit use of NSAIDs, including indomethacin extended-release capsules, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1). • Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
----------ADVERSE REACTIONS---------- Most common adverse reactions (incidence ≥ 3%) are headache, dizziness, dyspepsia and nausea. (6) To report SUSPECTED ADVERSE REACTIONS, contact Iroko Pharmaceuticals, LLC at 1-877-757-0676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.	**----------ADVERSE REACTIONS----------** Most common adverse reactions (incidence ≥ 3%) are headache, dizziness, dyspepsia and nausea. (6) **To report SUSPECTED ADVERSE REACTIONS, contact KVK-Tech, Inc. at 1-800-862-3895 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**		**----------ADVERSE REACTIONS----------** Most common adverse reactions (incidence ≥ 3%) are headache, dizziness, dyspepsia and nausea. (6) **To report SUSPECTED ADVERSE REACTIONS, contact KVK-Tech, Inc. at 1-800-862-3895 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**
----------DRUG INTERACTIONS---------- • Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking INDOCIN SR with drugs that interfere with hemostasis. Concomitant use of INDOCIN SR and analgesic doses of aspirin is not generally recommended (7) • ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with INDOCIN SR may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)	**----------DRUG INTERACTIONS-------** • Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking indomethacin extended-release capsules with drugs that interfere with hemostasis. Concomitant use of indomethacin extended-release capsules and analgesic doses of aspirin is not generally recommended (7) • ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with indomethacin extended-release capsules may diminish the		**----------DRUG INTERACTIONS---------** • Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking indomethacin extended-release capsules with drugs that interfere with hemostasis. Concomitant use of indomethacin extended-release capsules and analgesic doses of aspirin is not generally recommended (7) • ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with indomethacin extended-release capsules may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
• ACE Inhibitors and ARBs: Concomitant use with INDOCIN SR in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7) • Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7) • Digoxin: Concomitant use with INDOCIN SR can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)	antihypertensive effect of these drugs. Monitor blood pressure (7) • ACE Inhibitors and ARBs: Concomitant use with indomethacin extended-release capsules in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7) • Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7) • Digoxin: Concomitant use with indomethacin extended-release capsules can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)		• ACE Inhibitors and ARBs: Concomitant use with indomethacin extended-release capsules in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7) • Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7) • Digoxin: Concomitant use with indomethacin extended-release capsules can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)
----USE IN SPECIFIC POPULATIONS----- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of INDOCIN SR in women who have difficulties conceiving (8.3)	**-----USE IN SPECIFIC POPULATIONS----** Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of indomethacin extended-release capsules in women who have difficulties conceiving (8.3)		**------USE IN SPECIFIC POPULATIONS------** Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of indomethacin extended-release capsules in women who have difficulties conceiving (8.3)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.	**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**		**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
Revised 04/2021	**Revised 04/2021**	**2**	**Revised 07/2024**
FULL PRESCRIBING INFORMATION: CONTENTS*	**FULL PRESCRIBING INFORMATION: CONTENTS***		**FULL PRESCRIBING INFORMATION: CONTENTS***
WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS	**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**		**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**
1 INDICATIONS AND USAGE	**1 INDICATIONS AND USAGE**		**1 INDICATIONS AND USAGE**
2 DOSAGE AND ADMINISTRATION	**2 DOSAGE AND ADMINISTRATION**		**2 DOSAGE AND ADMINISTRATION**
2.1 General Dosing Instructions	2.1 General Dosing Instructions		2.1 General Dosing Instructions
2.2 Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis	2.2 Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis		2.2 Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis
2.3 Acute painful shoulder (bursitis and/or tendinitis)	2.3 Acute painful shoulder (bursitis and/or tendinitis)		2.3 Acute painful shoulder (bursitis and/or tendinitis)
3 DOSAGE FORMS AND STRENGTHS	**3 DOSAGE FORMS AND STRENGTHS**		**3 DOSAGE FORMS AND STRENGTHS**
4 CONTRAINDICATIONS	**4 CONTRAINDICATIONS**		**4 CONTRAINDICATIONS**
5 WARNINGS AND PRECAUTIONS	**5 WARNINGS AND PRECAUTIONS**		**5 WARNINGS AND PRECAUTIONS**
5.1 Cardiovascular Thrombotic Events	5.1 Cardiovascular Thrombotic Events		5.1 Cardiovascular Thrombotic Events
5.2 Gastrointestinal Bleeding, Ulceration, and Perforation			5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
5.3 Hepatotoxicity			5.3 Hepatotoxicity
5.4 Hypertension			5.4 Hypertension

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
5.5 Heart Failure and Edema	5.2 Gastrointestinal Bleeding, Ulceration, and Perforation		5.5 Heart Failure and Edema
5.6 Renal Toxicity and Hyperkalemia	5.3 Hepatotoxicity		5.6 Renal Toxicity and Hyperkalemia
5.7 Anaphylactic Reactions	5.4 Hypertension		5.7 Anaphylactic Reactions
5.8 Exacerbation of Asthma Related to Aspirin Sensitivity	5.5 Heart Failure and Edema		5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
5.9 Serious Skin Reactions	5.6 Renal Toxicity and Hyperkalemia		5.9 Serious Skin Reactions
5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	5.7 Anaphylactic Reactions		5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
5.11 Fetal Toxicity	5.8 Exacerbation of Asthma Related to Aspirin Sensitivity		5.11 Fetal Toxicity
5.12 Hematologic Toxicity	5.9 Serious Skin Reactions		5.12 Hematologic Toxicity
5.13 Masking of Inflammation and Fever	5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)		5.13 Masking of Inflammation and Fever
5.14 Laboratory Monitoring	5.11 Fetal Toxicity		5.14 Laboratory Monitoring
5.15 Central Nervous System Effects	5.12 Hematologic Toxicity		5.15 Central Nervous System Effects
5.16 Ocular Effects	5.13 Masking of Inflammation and Fever		5.16 Ocular Effects
6 **ADVERSE REACTIONS**	5.14 Laboratory Monitoring		6 **ADVERSE REACTIONS**
6.1 Clinical Trials Experience	5.15 Central Nervous System Effects	1	6.1 Clinical Trials Experience
7 **DRUG INTERACTIONS**	5.16 Ocular Effects		6.2 **Postmarketing Experience**
8 **USE IN SPECIFIC POPULATIONS**	6 **ADVERSE REACTIONS**		7 **DRUG INTERACTIONS**
8.1 Pregnancy	6.1 Clinical Trials Experience		8 **USE IN SPECIFIC POPULATIONS**
8.2 Lactation	7 **DRUG INTERACTIONS**		8.1 Pregnancy
8.3 Females and Males of Reproductive Potential	8 **USE IN SPECIFIC POPULATIONS**		8.2 Lactation
8.4 Pediatric Use	8.1 Pregnancy		8.3 Females and Males of Reproductive Potential
8.5 Geriatric Use			8.4 Pediatric Use
10 **OVERDOSAGE**			8.5 Geriatric Use

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
11 DESCRIPTION **12 CLINICAL PHARMACOLOGY** 12.1 Mechanism of Action 12.3 Pharmacokinetics 13 **NONCLINICAL TOXICOLOGY** 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility **14 CLINICAL STUDIES** **16 HOW SUPPLIED/STORAGE AND HANDLING** **17 PATIENT COUNSELING INFORMATION** * Sections or subsections omitted from the full prescribing information are not listed.	8.2 Lactation 8.3 Females and Males of Reproductive Potential 8.4 Pediatric Use 8.5 Geriatric Use **10 OVERDOSAGE** **11 DESCRIPTION** **12 CLINICAL PHARMACOLOGY** 12.1 Mechanism of Action 12.3 Pharmacokinetics **13 NONCLINICAL TOXICOLOGY** 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility **14 CLINICAL STUDIES** **16 HOW SUPPLIED/STORAGE AND HANDLING** **17 PATIENT COUNSELING INFORMATION** * Sections or subsections omitted from the full prescribing information are not listed.		**10 OVERDOSAGE** **11 DESCRIPTION** **12 CLINICAL PHARMACOLOGY** 12.1 Mechanism of Action 12.2 Pharmacokinetics **13 NONCLINICAL TOXICOLOGY** 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility **14 CLINICAL STUDIES** **16 HOW SUPPLIED/STORAGE AND HANDLING** **17 PATIENT COUNSELING INFORMATION** * Sections or subsections omitted from the full prescribing information are not listed.
FULL PRESCRIBING INFORMATION	**FULL PRESCRIBING INFORMATION**		**FULL PRESCRIBING INFORMATION**

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS **Cardiovascular Thrombotic Events** • **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].** • **• INDOCIN SR is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].** **Gastrointestinal Bleeding, Ulceration, and Perforation** • **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions* (*5.2*)].**	**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND ASTROINTESTINAL EVENTS** **Cardiovascular Thrombotic Events** • **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].** • **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].** **Gastrointestinal Bleeding, Ulceration, and Perforation** • **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These**		**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND ASTROINTESTINAL EVENTS** **Cardiovascular Thrombotic Events** • **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].** • **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].** **Gastrointestinal Bleeding, Ulceration, and Perforation** • **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use**

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
	events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions* (*5.2*)].		**and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions* (*5.2*)].**
1 INDICATIONS and USAGE	**1 INDICATIONS AND USAGE**		**1 INDICATIONS AND USAGE**
INDOCIN SR is indicated for: • Moderate to severe rheumatoid arthritis including acute flares of chronic disease • Moderate to severe ankylosing spondylitis • Moderate to severe osteoarthritis • Acute painful shoulder (bursitis and/or tendinitis)	Indomethacin extended-release capsules are indicated for: • Moderate to severe rheumatoid arthritis including acute flares of chronic disease • Moderate to severe ankylosing spondylitis • Moderate to severe osteoarthritis • Acute painful shoulder (bursitis and/or tendinitis)		Indomethacin extended-release capsules are indicated for: • Moderate to severe rheumatoid arthritis including acute flares of chronic disease • Moderate to severe ankylosing spondylitis • Moderate to severe osteoarthritis • Acute painful shoulder (bursitis and/or tendinitis)
2 DOSAGE AND ADMINISTRATION	**2 DOSAGE AND ADMINISTRATION**		**2 DOSAGE AND ADMINISTRATION**
2.1 General Dosing Instructions Carefully consider the potential benefits and risks of INDOCIN SR and other treatment options before deciding to use INDOCIN SR. Use the	**2.1 General Dosing Instructions** Carefully consider the potential benefits and risks of indomethacin extended-release capsules and other treatment options before		**2.1 General Dosing Instructions** Carefully consider the potential benefits and risks of indomethacin extended-release capsules and

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lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)]. After observing the response to initial therapy with indomethacin, the dose and frequency should be adjusted to suit an individual patient's needs. Adverse reactions generally appear to correlate with the dose of indomethacin. Therefore, every effort should be made to determine the lowest effective dosage for the individual patient. THIS SECTION PREDOMINANTLY REFERENCES THE INDOMETHACIN IMMEDIATE-RELEASE CAPSULE ORAL DOSAGE AND IS INTENDED TO PROVIDE GUIDANCE IN USING INDOCIN SR EXTENDED-RELEASE CAPSULES, 75 MG **INDOCIN SR, 75 mg once a day can be substituted for indomethacin immediate-release capsules, 25 mg three times a day. However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours [see Clinical Pharmacology (12)]. In addition, INDOCIN SR, 75 mg twice a day can be substituted for indomethacin immediate-release capsules, USP 50 mg three times a day.**	deciding to use indomethacin extended-release capsules. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*]. After observing the response to initial therapy with indomethacin, the dose and frequency should be adjusted to suit an individual patient's needs. Adverse reactions generally appear to correlate with the dose of indomethacin. Therefore, every effort should be made to determine the lowest effective dosage for the individual patient. THIS SECTION PREDOMINANTLY REFERENCES THE INDOMETHACIN IMMEDIATE-RELEASE CAPSULE ORAL DOSAGE AND IS INTENDED TO PROVIDE GUIDANCE IN USING INDOMETHACIN EXTENDED-RELEASE CAPSULES, 75 MG **Indomethacin extended-release capsules, 75 mg once a day can be substituted for indomethacin immediate-release capsules, 25 mg three times a day. However, there will be significant differences between the two dosage regimens in indomethacin blood**		other treatment options before deciding to use indomethacin extended-release capsules. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*]. After observing the response to initial therapy with indomethacin, the dose and frequency should be adjusted to suit an individual patient's needs. Adverse reactions generally appear to correlate with the dose of indomethacin. Therefore, every effort should be made to determine the lowest effective dosage for the individual patient. THIS SECTION PREDOMINANTLY REFERENCES THE INDOMETHACIN IMMEDIATE-RELEASE CAPSULE ORAL DOSAGE AND IS INTENDED TO PROVIDE GUIDANCE IN USING INDOMETHACIN EXTENDED-RELEASE CAPSULES, 75 MG **Indomethacin extended-release capsules, 75 mg once a day can be substituted for indomethacin immediate-release capsules, 25 mg three times a day. However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours [*see Clinical Pharmacology (12)*]. In addition, Indomethacin extended-release capsules, 75 mg twice a day can be substituted**

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INDOCIN SR may be substituted for all the indications for indomethacin immediate-release capsules, USP except acute gouty arthritis. Dosage Recommendations for Active Stages of the Following:	**levels, especially after 12 hours [*see Clinical Pharmacology (12)*]. In addition, Indomethacin extended-release capsules, 75 mg twice a day can be substituted for indomethacin immediate-release capsules, USP 50 mg three times a day.** **Indomethacin extended-release capsules may be substituted for all the indications for indomethacin immediate-release capsules, USP except acute gouty arthritis.** Dosage Recommendations for Active Stages of the Following:		**for indomethacin immediate-release capsules, USP 50 mg three times a day.** **Indomethacin extended-release capsules may be substituted for all the indications for indomethacin immediate-release capsules, USP except acute gouty arthritis.** Dosage Recommendations for Active Stages of the Following:
2.2 Moderate to severe rheumatoid arthritis including acute flares ofchronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis Indomethacin immediate-release capsules, 25 mg twice a day or three times a day. If this is well tolerated, increase the daily dosage by 25 mg or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150 -200 mg is reached. Doses above this amount generally do not increase the effectiveness of the drug. In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up	**2.2 Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis** Indomethacin immediate-release capsules, 25 mg twice a day or three times a day. If this is well tolerated, increase the daily dosage by 25 mg or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150 - 200 mg is reached. Doses above this amount generally do not increase the effectiveness of the drug.		**2.2 Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis** Indomethacin immediate-release capsules, 25 mg twice a day or three times a day. If this is well tolerated, increase the daily dosage by 25 mg or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150 - 200 mg is reached. Doses above this amount generally do not increase the effectiveness of the drug.

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to a maximum of 100 mg, of the total daily dose at bedtime may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily. If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and observe the patient closely. If severe adverse reactions occur, stop the drug. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions. As advancing years appear to increase the possibility of adverse reactions, INDOCIN SR should be used with greater care in the elderly [see *Use in Specific Populations (8.5)*].	In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily. If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and observe the patient closely. If severe adverse reactions occur, stop the drug. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin extended-release capsules should be used with greater care in the elderly [*see Use in Specific Populations (8.5)*].		In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily. If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and observe the patient closely. If severe adverse reactions occur, stop the drug. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin extended-release capsules should be used with greater care in the elderly [*see Use in Specific Populations (8.5)*].

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2.3 Acute painful shoulder (bursitis and/or tendinitis) Indomethacin immediate-release capsules 75-150 mg daily in 3 or 4 divided doses. Discontinue INDOCIN SR treatment after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.	**2.3 Acute painful shoulder (bursitis and/or tendinitis)** Indomethacin immediate-release capsules 75-150 mg daily in 3 or 4 divided doses. Discontinue indomethacin extended-release capsules treatment after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.		**2.3 Acute painful shoulder (bursitis and/or tendinitis)** Indomethacin immediate-release capsules 75-150 mg daily in 3 or 4 divided doses. Discontinue indomethacin extended-release capsules treatment after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.
3 DOSAGE FORMS AND STRENGTHS INDOCIN SR (indomethacin) extended-release capsules 75 mg -opaque blue cap and clear body hard shell gelatin capsules, containing a mixture of blue and white pellets, printed with both 157 and WPPh.	**3 DOSAGE FORMS AND STRENGTHS** Indomethacin Extended-release Capsules USP 75 mg - yellow opaque cap, natural body with black imprint "K 16" on both cap and body, filled with white pellets.		**3 DOSAGE FORMS AND STRENGTHS** Indomethacin Extended-release Capsules USP 75 mg - yellow opaque cap, natural body with black imprint "K 16" on both cap and body, filled with white pellets.
4 CONTRAINDICATIONS INDOCIN SR is contraindicated in the following patients:	**4 CONTRAINDICATIONS** Indomethacin extended-release capsules are contraindicated in the following patients:		**4 CONTRAINDICATIONS** Indomethacin extended-release capsules are contraindicated in the following patients:

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• Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*] • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*] • In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]	• Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*] • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*] • In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]		• Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*] • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*] • In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]
5 WARNINGS AND PRECAUTIONS	**5 WARNINGS AND PRECAUTIONS**		**5 WARNINGS AND PRECAUTIONS**
5.1 Cardiovascular Thrombotic Events Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV	**5.1 Cardiovascular Thrombotic Events** Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without		**5.1 Cardiovascular Thrombotic Events** Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV

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disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as indomethacin, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*]. <u>Status Post Coronary Artery Bypass Graft (CABG) Surgery</u>	known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as indomethacin, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].		disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as indomethacin, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*]. <u>Status Post Coronary Artery Bypass Graft (CABG) Surgery</u>

RLD Label **Indocin SR (Zyla Life Sciences)** **(Reference ID: 4786622)**	**KVK-Tech's Pack Insert** **(Item Id # 6030/08)**		**KVK-Tech's Pack Insert** **(Item Id # 6030/09)**
Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*]. Post-MI Patients Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up. Avoid the use of INDOCIN SR in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If INDOCIN SR is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.	Status Post Coronary Artery Bypass Graft (CABG) Surgery Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*]. Post-MI Patients Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up. Avoid the use of indomethacin extended-release capsules in patients with a recent MI unless the benefits are expected to outweigh		Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*]. Post-MI Patients Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up. Avoid the use of indomethacin extended-release capsules in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If indomethacin extended-release capsules are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

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	the risk of recurrent CV thrombotic events. If indomethacin extended-release capsules are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.		
5.2 Gastrointestinal Bleeding, Ulceration, and Perforation NSAIDs, including indomethacin, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk. <u>Risk Factors for GI Bleeding, Ulceration, and Perforation</u> Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater	**5.2 Gastrointestinal Bleeding, Ulceration, and Perforation** NSAIDs, including indomethacin, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk. <u>Risk Factors for GI Bleeding, Ulceration, and Perforation</u>		**5.2 Gastrointestinal Bleeding, Ulceration, and Perforation** NSAIDs, including indomethacin, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk. <u>Risk Factors for GI Bleeding, Ulceration, and Perforation</u> Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater

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than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding. <u>Strategies to Minimize the GI Risks in NSAID-treated patients:</u> • Use the lowest effective dosage for the shortest possible duration. • Avoid administration of more than one NSAID at a time. • Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs. • Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy. • If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and	Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding. <u>Strategies to Minimize the GI Risks in NSAID-treated patients:</u> • Use the lowest effective dosage for the shortest possible duration. • Avoid administration of more than one NSAID at a time. • Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies		than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding. <u>Strategies to Minimize the GI Risks in NSAID-treated patients:</u> • Use the lowest effective dosage for the shortest possible duration. • Avoid administration of more than one NSAID at a time. • Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs. • Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.

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discontinue INDOCIN SR until a serious GI adverse event is ruled out. • In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].	other than NSAIDs. • Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy. • If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue indomethacin extended-release capsules until a serious GI adverse event is ruled out. • In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].		• If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue indomethacin extended-release capsules until a serious GI adverse event is ruled out. • In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].
5.3 Hepatotoxicity Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.	**5.3 Hepatotoxicity** Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.		**5.3 Hepatotoxicity** Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

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Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including indomethacin. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue INDOCIN SR immediately, and perform a clinical evaluation of the patient.	Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including indomethacin. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue indomethacin extended-release capsules immediately, and perform a clinical evaluation of the patient.		Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including indomethacin. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue indomethacin extended-release capsules immediately, and perform a clinical evaluation of the patient.
5.4 Hypertension NSAIDs, including INDOCIN SR, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].	**5.4 Hypertension** NSAIDs, including indomethacin extended-release capsules, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these		**5.4 Hypertension** NSAIDs, including indomethacin extended-release capsules, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these

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Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.	therapies when taking NSAIDs [*see Drug Interactions (7)*]. Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.		therapies when taking NSAIDs [*see Drug Interactions (7)*]. Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.
5.5 Heart Failure and Edema The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of indomethacin may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].	**5.5 Heart Failure and Edema** The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of indomethacin may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].		**5.5 Heart Failure and Edema** The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of indomethacin may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

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Avoid the use of INDOCIN SR in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If INDOCIN SR is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.	Avoid the use of indomethacin extended-release capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If indomethacin extended-release capsules are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.		Avoid the use of indomethacin extended-release capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If indomethacin extended-release capsules are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.
5.6 Renal Toxicity and Hyperkalemia Renal Toxicity Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is	**5.6 Renal Toxicity and Hyperkalemia** Renal Toxicity Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly.		**5.6 Renal Toxicity and Hyperkalemia** Renal Toxicity Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is

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usually followed by recovery to the pretreatment state. No information is available from controlled clinical studies regarding the use of INDOCIN SR in patients with advanced renal disease. The renal effects of INDOCIN SR may hasten the progression of renal dysfunction in patients with preexisting renal disease. Correct volume status in dehydrated or hypovolemic patients prior to initiating INDOCIN SR. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of INDOCIN SR [*see Drug Interactions (7)*]. Avoid the use of INDOCIN SR in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If INDOCIN SR is used in patients with advanced renal disease, monitor patients for signs of worsening renal function. It has been reported that the addition of the potassium-sparing diuretic, triamterene, to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together. <u>Hyperkalemia</u>	Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. No information is available from controlled clinical studies regarding the use of indomethacin extended-release capsules in patients with advanced renal disease. The renal effects of indomethacin extended-release capsules may hasten the progression of renal dysfunction in patients with preexisting renal disease. Correct volume status in dehydrated or hypovolemic patients prior to initiating indomethacin extended-release capsules. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of indomethacin extended-release capsules [*see Drug Interactions (7)*]. Avoid the use of indomethacin extended-release capsules in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If indomethacin extended-release capsules are used in patients with advanced renal disease, monitor patients for signs of worsening renal function. It has been reported that the addition of the potassium-sparing diuretic, triamterene, to a maintenance schedule of indomethacin		usually followed by recovery to the pretreatment state. No information is available from controlled clinical studies regarding the use of indomethacin extended-release capsules in patients with advanced renal disease. The renal effects of indomethacin extended-release capsules may hasten the progression of renal dysfunction in patients with preexisting renal disease. Correct volume status in dehydrated or hypovolemic patients prior to initiating indomethacin extended-release capsules. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of indomethacin extended-release capsules [*see Drug Interactions (7)*]. Avoid the use of indomethacin extended-release capsules in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If indomethacin extended-release capsules are used in patients with advanced renal disease, monitor patients for signs of worsening renal function. It has been reported that the addition of the potassium-sparing diuretic, triamterene, to a maintenance schedule of indomethacin resulted in

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Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state. Both Indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.	resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together. Hyperkalemia Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state. Both Indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.		reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together. Hyperkalemia Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state. Both Indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.
5.7 Anaphylactic Reactions Indomethacin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to indomethacin and in patients with aspirin-sensitive asthma [see *Contraindications (4) and Warnings and Precautions (5.8)*].	**5.7 Anaphylactic Reactions** Indomethacin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to indomethacin and in patients with aspirin-		**5.7 Anaphylactic Reactions** Indomethacin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to indomethacin and in patients with aspirin-sensitive asthma [*see*

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Seek emergency help if an anaphylactic reaction occurs.	sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*]. Seek emergency help if an anaphylactic reaction occurs.		*Contraindications (4) and Warnings and Precautions (5.8)*]. Seek emergency help if an anaphylactic reaction occurs.
5.8 Exacerbation of Asthma Related to Aspirin Sensitivity A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, INDOCIN SR is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When INDOCIN SR is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.	**5.8 Exacerbation of Asthma Related to Aspirin Sensitivity** A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, indomethacin extended-release capsules are contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When indomethacin extended-release capsules are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.		**5.8 Exacerbation of Asthma Related to Aspirin Sensitivity** A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, indomethacin extended-release capsules are contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When indomethacin extended-release capsules are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.
5.9 Serious Skin Reactions NSAIDs, including indomethacin, can cause serious skin adverse reactions such as exfoliative	**5.9 Serious Skin Reactions** NSAIDs, including indomethacin, can cause serious skin adverse reactions such as		**5.9 Serious Skin Reactions** NSAIDs, including indomethacin, can cause serious skin adverse reactions such as exfoliative

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dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of INDOCIN SR at the first appearance of skin rash or any other sign of hypersensitivity. INDOCIN SR is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].	exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of indomethacin extended-release capsules at the first appearance of skin rash or any other sign of hypersensitivity. Indomethacin extended-release capsules are contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].	1	dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of indomethacin extended-release capsules at the first appearance of skin rash or any other sign of hypersensitivity. Indomethacin extended-release capsules are contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].
5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as INDOCIN SR. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other	**5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as indomethacin extended-release capsules. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present.		**5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as indomethacin extended-release capsules. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems

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organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue INDOCIN SR and evaluate the patient immediately.	Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue indomethacin extended-release capsules and evaluate the patient immediately.		not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue indomethacin extended-release capsules and evaluate the patient immediately.
5.11 Fetal Toxicity Premature Closure of Fetal Ductus Arteriosus Avoid use of NSAIDs, including INDOCIN SR, in pregnant women at about 30 weeks of gestation and later. NSAIDs, including INDOCIN SR, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age. Oligohydramnios/Neonatal Renal Impairment Use of NSAIDs, including INDOCIN SR, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although	**5.11 Fetal Toxicity** Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs, including indomethacin extended-release capsules, in pregnant women at about 30 weeks gestation and later. NSAIDs, including indomethacin extended-release capsules, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age. Oligohydramnios/Neonatal Renal Impairment: Use of NSAIDs, including indomethacin extended-release capsules, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios		**5.11 Fetal Toxicity** Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs, including indomethacin extended-release capsules, in pregnant women at about 30 weeks gestation and later. NSAIDs, including indomethacin extended-release capsules, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age. Oligohydramnios/Neonatal Renal Impairment: Use of NSAIDs, including indomethacin extended-release capsules, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes

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oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit INDOCIN SR use to the lowest effective dose and shortest duration possssible. Consider ultrasound monitoring of amniotic fluid if INDOCIN SR treatment extends beyond 48 hours. Discontinue INDOCIN SR if oligohydramnios occurs and follow up according to clinical practice [see *Use in Specific Populations (8.1)*].	and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit indomethacin extended-release capsules use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if indomethacin extended-release capsules treatment extends beyond 48 hours. Discontinue indomethacin extended-release capsules if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].		are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit indomethacin extended-release capsules use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if indomethacin extended-release capsules treatment extends beyond 48 hours. Discontinue indomethacin extended-release capsules if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].
5.12 Hematologic Toxicity Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid	**5.12 Hematologic Toxicity** Anemia has occurred in NSAID-treated patients. This may be due to occult or gross		**5.12 Hematologic Toxicity** Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid

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retention, or an incompletely described effect on erythropoiesis. If a patient treated with INDOCIN SR has any signs or symptoms of anemia, monitor hemoglobin or hematocrit. NSAIDs, including INDOCIN SR, may increase the risk of bleeding events. Co-morbid conditions, such as coagulation disorders, or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].	blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with indomethacin extended-release capsules has any signs or symptoms of anemia, monitor hemoglobin or hematocrit. NSAIDs, including indomethacin extended-release capsules, may increase the risk of bleeding events. Co-morbid conditions, such as coagulation disorders, or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].		retention, or an incompletely described effect on erythropoiesis. If a patient treated with indomethacin extended-release capsules has any signs or symptoms of anemia, monitor hemoglobin or hematocrit. NSAIDs, including indomethacin extended-release capsules, may increase the risk of bleeding events. Co-morbid conditions, such as coagulation disorders, or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].
5.13 Masking of Inflammation and Fever The pharmacological activity of INDOCIN SR in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.	**5.13 Masking of Inflammation and Fever** The pharmacological activity of indomethacin extended-release capsules in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.		**5.13 Masking of Inflammation and Fever** The pharmacological activity of indomethacin extended-release capsules in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.
5.14 Laboratory Monitoring Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms	**5.14 Laboratory Monitoring** Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning		**Laboratory Monitoring** Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term

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or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].	symptoms or signs, consider monitoring patients on long-term NSAID treatment with CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].		NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].
5.15 Central Nervous System Effects INDOCIN SR may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. Discontinue INDOCIN SR if severe CNS adverse reactions develop. INDOCIN SR may cause drowsiness; therefore, caution patients about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with INDOCIN SR.	**5.15 Central Nervous System Effects** Indomethacin extended-release capsules may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. Discontinue indomethacin extended-release capsules if severe CNS adverse reactions develop. Indomethacin extended-release capsules may cause drowsiness; therefore, caution patients about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin extended-release capsules.		**5.15 Central Nervous System Effects** Indomethacin extended-release capsules may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. Discontinue indomethacin extended-release capsules if severe CNS adverse reactions develop. Indomethacin extended-release capsules may cause drowsiness; therefore, caution patients about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin extended-release capsules.
5.16 Ocular Effects Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with INDOCIN SR. Be alert to the possible association between the changes noted and INDOCIN SR. It is	**5.16 Ocular Effects** Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin extended-release capsules. Be alert to the		**5.16 Ocular Effects** Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin extended-release capsules. Be alert to the possible association between the changes noted

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advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. INDOCIN SR is not indicated for long-term treatment.	possible association between the changes noted and indomethacin extended-release capsules. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. Indomethacin extended-release capsules are not indicated for long-term treatment.		and indomethacin extended-release capsules. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. Indomethacin extended-release capsules are not indicated for long-term treatment.
ADVERSE REACTIONS The following adverse reactions are discussed in greater detail in other sections of the labeling: • Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*] • GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*] • Hepatotoxicity [*see Warnings and Precautions (5.3)*] • Hypertension [*see Warnings and Precautions (5.4)*] • Heart Failure and Edema [*see Warnings and Precautions (5.5)*]	**6 ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the labeling: • Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*] • GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*] • Hepatotoxicity [*see Warnings and Precautions (5.3)*] • Hypertension [*see Warnings and Precautions (5.4)*] • Heart Failure and Edema [*see Warnings and Precautions (5.5)*] • Renal Toxicity and Hyperkalemia [*see*		**6 ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the labeling: • Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*] • GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*] • Hepatotoxicity [*see Warnings and Precautions (5.3)*] • Hypertension [*see Warnings and Precautions (5.4)*] • Heart Failure and Edema [*see Warnings and Precautions (5.5)*] • Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]

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• Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*] • Anaphylactic Reactions [*see Warnings and Precautions (5.7)*] • Serious Skin Reactions [*see Warnings and Precautions (5.9)*] • Hematologic Toxicity [*see Warnings and Precautions (5.11)*]	*Warnings and Precautions (5.6)*] • Anaphylactic Reactions [*see Warnings and Precautions (5.7)*] • Serious Skin Reactions [*see Warnings and Precautions (5.9)*] • Hematologic Toxicity [*see Warnings and Precautions (5.12)*]		• Anaphylactic Reactions [*see Warnings and Precautions (5.7)*] • Serious Skin Reactions [*see Warnings and Precautions (5.9)*] • Hematologic Toxicity [*see Warnings and Precautions (5.12)*]
6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving indomethacin immediate-release capsules than in the group taking indomethacin suppositories or placebo. In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal	**6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving indomethacin immediate-release capsules than in the group taking indomethacin suppositories or placebo. In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with indomethacin immediate-release capsules or suppositories was comparable. The incidence		**6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving indomethacin immediate-release capsules than in the group taking indomethacin suppositories or placebo. In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with indomethacin immediate-release capsules or suppositories was comparable. The incidence of

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adverse effects with indomethacin immediate-release capsules or suppositories was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group. The adverse reactions for indomethacin immediate-release capsules listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between INDOCIN and these adverse reactions, some of which have been reported only rarely. The adverse reactions reported with indomethacin immediate-release capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the capsules. **Table 1 Summary of Adverse Reactions for INDOCIN Capsules**	of lower gastrointestinal adverse effects was greater in the suppository group. The adverse reactions for indomethacin immediate-release capsules listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely. The adverse reactions reported with indomethacin immediate-release capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the capsules. **Table 1 Summary of Adverse Reactions for Indomethacin Capsules**		lower gastrointestinal adverse effects was greater in the suppository group. The adverse reactions for indomethacin immediate-release capsules listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely. The adverse reactions reported with indomethacin immediate-release capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the capsules. **Table 1 Summary of Adverse Reactions for Indomethacin Capsules**

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)		
Incidence greater than 1%	***Incidence less than 1%***	
GASTROINTESTINAL		
nausea * with or without vomiting dyspepsia* (including indigestion, heartburn and epigastric pain) diarrhea abdominal distress or pain constipation	anorexia bloating (includes distension) flatulence peptic ulcer gastroenteritis rectal bleeding proctitis single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines	gastrointestinal bleeding without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis ulcerative stomatitis toxic

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Incidence greater than 1%	***Incidence less than 1%***	
GASTROINTESTINAL		
nausea * with or without vomiting dyspepsia * (including indigestion, heartburn and epigastric pain) diarrhea abdominal distress or pain constipation	anorexia bloating (includes distension) flatulence peptic ulcer gastroenteritis rectal bleeding proctitis single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines intestinal ulceration	gastrointestinal bleeding without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis ulcerative stomatitis toxic hepatitis

KVK-Tech's Pack Insert (Item Id # 6030/09)		
Incidence greater than 1%	***Incidence less than 1%***	
GASTROINTESTINAL		
nausea * with or without vomiting dyspepsia * (including indigestion, heartburn and epigastric pain) diarrhea abdominal distress or pain constipation	anorexia bloating (includes distension) flatulence peptic ulcer gastroenteritis rectal bleeding proctitis single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines intestinal ulceration associated with stenosis	gastrointestinal bleeding without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis ulcerative stomatitis toxic

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)			KVK-Tech's Pack Insert (Item Id # 6030/08)				KVK-Tech's Pack Insert (Item Id # 6030/09)		
	intestinal ulceration associated with stenosis and obstruction	hepatitis and jaundice (some fatal cases have been reported) intestinal strictures (diaphragms) pancreatitis		associated with stenosis and obstruction	and jaundice (some fatal cases have been reported) intestinal strictures (diaphragms) pancreatitis			and obstruction	hepatitis and jaundice (some fatal cases have been reported) intestinal strictures (diaphragms) pancreatitis
CENTRAL NERVOUS SYSTEM			*CENTRAL NERVOUS SYSTEM*				*CENTRAL NERVOUS SYSTEM*		
headache (11.7%) dizziness* vertigo somnolence depression and fatigue (including malaise and listlessness)	anxiety (includes nervousness) muscle weakness involuntary muscle movements insomnia muzziness psychic disturbances including psychotic episodes mental	light-headedness syncope paresthesia aggravation of epilepsy and parkinsonism depersonalization coma peripheral neuropathy convulsion dysarthria	headache (11.7%) dizziness* vertigo somnolence depression and fatigue (including malaise and listlessness)	anxiety (includes nervousness) muscle weakness involuntary muscle movements insomnia muzziness psychic disturbances including psychotic episodes mental	light-headedness syncope paresthesia aggravation of epilepsy and parkinsonism depersonalization coma peripheral neuropathy convulsion dysarthria		headache (11.7%) dizziness* vertigo somnolence depression and fatigue (including malaise and	anxiety (includes nervousness) muscle weakness involuntary muscle movements insomnia muzziness psychic disturbances including psychotic	light-headedness syncope paresthesia aggravation of epilepsy and parkinsonism depersonalization coma peripheral neuropathy

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)			KVK-Tech's Pack Insert (Item Id # 6030/08)			KVK-Tech's Pack Insert (Item Id # 6030/09)		
	confusion drowsiness			confusion drowsiness		listlessn ess)	episodes mental confusion drowsiness	convulsion dysarthria
SPECIAL SENSES			*SPECIAL SENSES*			*SPECIAL SENSES*		
tinnitus	ocular — corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with INDOCIN	blurred vision diplopia hearing disturbances, deafness	tinnitus	ocular - corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin	blurred vision diplopia hearing disturbances, deafness	tinnitus	ocular - corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin	blurred vision diplopia hearing disturbances , deafness
CARDIOVASCULAR			*CARDIOVASCULAR*			*CARDIOVASCULAR*		
None	hypertension hypotension tachycardia chest pain	congestive heart failure arrhythmia; palpitations	None	hypertension hypotension tachycardia chest pain	congestive heart failure arrhythmia; palpitations	None	hypertension hypotension tachycardia chest pain	congestive heart failure arrhythmia; palpitations
METABOLIC			*METABOLIC*			*METABOLIC*		
None	edema weight gain fluid retention	hyperglycem ia glycosuria	None	edema weight gain fluid retention flushing or	hyperglycemi a glycosuria hyperkalemia	None	edema weight gain fluid retention flushing or	hyperglyce mia glycosuria hyperkalemi

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)			KVK-Tech's Pack Insert (Item Id # 6030/08)			KVK-Tech's Pack Insert (Item Id # 6030/09)		
	flushing or sweating	hyperkalemia		sweating			sweating	a
INTEGUMENTARY			*INTEGUMENTARY*			*INTEGUMENTARY*		
none	pruritus rash; urticaria petechiae or ecchymosis	exfoliative dermatitis erythema nodosum loss of hair Stevens-Johnson syndrome erythema multiforme toxic epidermal necrolysis	none	pruritus rash; urticaria petechiae or ecchymosis	exfoliative dermatitis erythema nodosum loss of hair Stevens-Johnson syndrome erythema multiforme toxic epidermal necrolysis	none	pruritus rash; urticaria petechiae or ecchymosis	exfoliative dermatitis erythema nodosum loss of hair Stevens-Johnson syndrome erythema multiforme toxic epidermal necrolysis
HEMATOLOGIC			*HEMATOLOGIC*			*HEMATOLOGIC*		
None	leukopenia bone marrow depression anemia secondary to obvious or occult gastrointestinal bleeding	aplastic anemia hemolytic anemia agranulocytosis thrombocytopenic purpura disseminated	None	leukopenia bone marrow depression anemia secondary to obvious or occult gastrointestinal bleeding	aplastic anemia hemolytic anemia agranulocytosis thrombocytopenic purpura disseminated intravascular coagulation	None	leukopenia bone marrow depression anemia secondary to obvious or occult gastrointestinal bleeding	aplastic anemia hemolytic anemia agranulocytosis thrombocytopenic purpura disseminated intravascular coagulation
						HYPERSENSITIVITY		

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)	KVK-Tech's Pack Insert (Item Id # 6030/09)
intravascular coagulation	*HYPERSENSITIVITY*	None acute anaphylaxis acute respiratory distress rapid fall in blood pressure resembling a shock-like state angioedema dyspnea asthma purpura angiitis pulmonary edema fever
HYPERSENSITIVITY	None acute anaphylaxis acute respiratory distress rapid fall in blood pressure resembling a shock-like state angioedema dyspnea asthma purpura angiitis pulmonary edema fever	*GENITOURINARY*
None acute anaphylaxis acute respiratory distress rapid fall in blood pressure resembling a shock-like state angioedema dyspnea asthma purpura angiitis pulmonary edema fever	*GENITOURINARY*	None hematuria vaginal bleeding proteinuria nephrotic syndrome interstitial nephritis BUN elevation renal insufficiency, including renal failure
GENITOURINARY	None hematuria vaginal bleeding proteinuria nephrotic syndrome interstitial nephritis BUN elevation renal insufficiency, including renal failure	*MISCELLANEOUS*
Incidence greater than 1% *Incidence less than 1%*	*MISCELLANEOUS*	None epistaxis breast changes, including enlargement and tenderness, or gynecomastia
None hematuria vaginal bleeding proteinuria nephrotic syndrome interstitial nephritis BUN elevation renal insufficiency, including renal failure	None epistaxis breast changes, including enlargement and tenderness,	* Reactions occurring in 3% to 9% of patients
MISCELLANEOUS		

RLD Label Indocin SR (Zyla Life Sciences) (Reference ID: 4786622)	KVK-Tech's Pack Insert (Item Id # 6030/08)		KVK-Tech's Pack Insert (Item Id # 6030/09)
None	epistaxis breast changes, including enlargement and tenderness, or gynecomastia		
* Reactions occurring in 3% to 9% of patients treated with INDOCIN. (Those reactions occurring in less than 3% of the patients are unmarked.)			
Causal relationship unknown: Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians: *Cardiovascular*: Thrombophlebitis *Hematologic*: Although there have been several reports of leukemia, the supporting information is weak *Genitourinary*: Urinary frequency A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group Aβ hemolytic streptococcus, has been described in			
	or gynecomastia		treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked.)
	* Reactions occurring in 3% to 9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked.)		
	Causal relationship unknown: Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians: *Cardiovascular:* Thrombophlebitis *Hematologic:* Although there have been several reports of leukemia, the supporting information is weak *Genitourinary:* Urinary frequency A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group Aβ hemolytic streptococcus, has been described in persons treated with nonsteroidal		**Causal relationship unknown:** Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians: *Cardiovascular:* Thrombophlebitis *Hematologic:* Although there have been several reports of leukemia, the supporting information is weak *Genitourinary:* Urinary frequency A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group Aβ hemolytic streptococcus, has been described in persons treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome.

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persons treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome.	anti-inflammatory agents, including indomethacin, sometimes with fatal outcome.		
		1	**6.2 Postmarketing Experience** **The following adverse reactions have been identified during post approval use of indomethacin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.** **Skin and Appendages: Exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE).**
7 DRUG INTERACTIONS	**7 DRUG INTERACTIONS**		**7 DRUG INTERACTIONS**

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See Table 2 for clinically significant drug interactions with indomethacin.

Table 2 Clinically Significant Drug Interactions with Indomethacin

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of INDOCIN SR with anticoagulants (e.g.,

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See Table 2 for clinically significant drug interactions with indomethacin.

Table 2 Clinically Significant Drug Interactions with Indomethacin

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of

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See Table 2 for clinically significant drug interactions with indomethacin.

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Drugs That Interfere with Hemostasis	
Clinical Impact:	• Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of indomethacin extended-release capsules with anticoagulants (e.g.,

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	warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.11)*].		indomethacin extended-release capsules with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.12)*].		warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.12)*].
Aspirin		**Aspirin**		**Aspirin**	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].	*Clinical Impact:*	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].	*Clinical Impact:*	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of INDOCIN SR and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.11)*]. INDOCIN SR is not a substitute for low dose	*Intervention:*	Concomitant use of indomethacin extended-release capsules and analgesic doses of aspirin is	*Intervention:*	Concomitant use of indomethacin extended-release capsules and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.12)*]. Indomethacin extended-release capsules is not a

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	aspirin for cardiovascular protection.		not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.12)*]. Indomethacin extended-release capsules is not a substitute for low dose aspirin for cardiovascular protection.		substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers		**ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers**		**ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers**	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.	*Clinical Impact:*	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.	*Clinical Impact:*	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of INDOCIN SR and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the			*Intervention:*	• During concomitant use of

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	desired blood pressure is obtained. • During concomitant use of INDOCIN SR and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.	*Interventi on:*	• During concomitant use of indomethacin extended-release capsules and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of indomethacin extended-release capsules and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.		indomethacin extended-release capsules and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of indomethacin extended-release capsules and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics		**Diuretics**			**Diuretics**	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the	*Clinical Impact:*	Clinical studies, as well as post-marketing		*Clinical Impact:*	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some

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	natriuretic effect of loop diuretic (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. It has been reported that the addition of triamterene to a maintenance schedule of INDOCIN SR resulted in reversible acute renal failure in two of four healthy volunteers. INDOCIN SR and triamterene should not be administered together. Both INDOCIN SR and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of INDOCIN SR and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.		observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. It has been reported that the addition of triamterene to a maintenance schedule of indomethacin extended-release capsules resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin extended-release capsules and triamterene should not be administered together. Both indomethacin extended-release capsules and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin extended-release capsules and potassium-sparing diuretics on potassium levels and renal function should be considered when these		patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. It has been reported that the addition of triamterene to a maintenance schedule of indomethacin extended-release capsules resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin extended-release capsules and triamterene should not be administered together. Both indomethacin extended-release capsules and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin extended-release capsules and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently.
Interventi on:	Indomethacin and triamterene should not be administered together. During concomitant use of INDOCIN SR with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy			*Intervention :*	Indomethacin and triamterene should not be administered together. During concomitant use of

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	including antihypertensive effects. Be aware that indomethacin and potassium-sparing diuretics may both be associated with increased serum potassium levels [*see Warnings and Precautions (5.6)*].		agents are administered concurrently.		indomethacin extended-release capsules with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. Be aware that indomethacin and potassium-sparing diuretics may both be associated with increased serum potassium levels [*see Warnings and Precautions (5.6)*].
		Interventi on:	Indomethacin and triamterene should not be administered together. During concomitant use of indomethacin extended-release capsules with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. Be aware that indomethacin and potassium-sparing diuretics may both be associated with increased serum potassium levels [*see Warnings and Precautions (5.6)*].		
Digoxin		**Digoxin**		**Digoxin**	
Clinical Impact:	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.	*Clinical Impact:*	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.	*Clinical Impact:*	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Interventi on:	During concomitant use of INDOCIN SR and digoxin, monitor serum digoxin levels.	*Interventi on:*	During concomitant use of indomethacin extended-release capsules and digoxin, monitor serum digoxin levels.	*Intervention :*	During concomitant use of indomethacin extended-release capsules and digoxin, monitor serum digoxin levels.
Lithium				**Lithium**	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal				

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	lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.	**Lithium**			*Clinical Impact:*	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of INDOCIN SR and lithium, monitor patients for signs of lithium toxicity.	*Clinical Impact:*	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.		*Intervention:*	During concomitant use of indomethacin extended-release capsules and lithium, monitor patients for signs of lithium toxicity.
Methotrexate		*Intervention:*	During concomitant use of indomethacin extended-release capsules and lithium, monitor patients for signs of lithium toxicity.		**Methotrexate**	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).	**Methotrexate**			*Clinical Impact:*	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of INDOCIN SR and methotrexate, monitor patients for methotrexate toxicity.	*Clinical Impact:*	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).		*Intervention:*	During concomitant use of indomethacin extended-release capsules and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine		*Intervention:*	During concomitant use of indomethacin extended-release capsules and methotrexate, monitor patients for methotrexate toxicity.		**Cyclosporine**	
Clinical Impact:	Concomitant use of INDOCIN SR and cyclosporine may increase cyclosporine's nephrotoxicity.	**Cyclosporine**				

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Interventi on:	During concomitant use of INDOCIN SR and cyclosporine, monitor patients for signs of worsening renal function.	*Clinical Impact:*	Concomitant use of indomethacin extended-release capsules and cyclosporine may increase cyclosporine's nephrotoxicity.	*Clinical Impact:*	Concomitant use of indomethacin extended-release capsules and cyclosporine may increase cyclosporine's nephrotoxicity.
		Interventi on:	During concomitant use of indomethacin extended-release capsules and cyclosporine, monitor patients for signs of worsening renal function.	*Intervention :*	During concomitant use of indomethacin extended-release capsules and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates		**NSAIDs and Salicylates**		**NSAIDs and Salicylates**	
Clinical Impact:	Concomitant use of indomethacin with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)]*. Combined use with diflunisal may be particularly hazardous because diflunisal causes significantly higher plasma levels of indomethacin. [see *Clinical Pharmacology (12.3)*]. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage.	*Clinical Impact:*	Concomitant use of indomethacin with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)]*. Combined use with diflunisal may be particularly hazardous because diflunisal causes significantly higher plasma levels of indomethacin [see *Clinical Pharmacology (12.3)*]. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal	*Clinical Impact:*	Concomitant use of indomethacin with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)]*. Combined use with diflunisal may be particularly hazardous because diflunisal causes significantly higher plasma levels of indomethacin [see *Clinical Pharmacology (12.3)*]. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage.
Interventi on:	The concomitant use of indomethacin with other NSAIDs or salicylates, especially diflunisal, is not recommended.			*Intervention:*	The concomitant use of indomethacin with other

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			hemorrhage.		NSAIDs or salicylates, especially diflunisal, is not recommended.
Pemetrexed		*Interventi on:*	The concomitant use of indomethacin with other NSAIDs or salicylates, especially diflunisal, is not recommended.	**Pemetrexed**	
Clinical Impact:	Concomitant use of INDOCIN SR and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).	**Pemetrexed**		*Clinical Impact:*	Concomitant use of indomethacin extended-release capsules and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Interventi on:	During concomitant use of INDOCIN SR and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives	*Clinical Impact:*	Concomitant use of indomethacin extended-release capsules and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).	*Intervention:*	During concomitant use of indomethacin extended-release capsules and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of,
		Interventi on:	During concomitant use of indomethacin extended-release capsules and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a		

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	(e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.		period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.		and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Probenecid		**Probenecid**		**Probenecid**	
Clinical Impact:	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.	*Clinical Impact:*	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.	*Clinical Impact:*	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.
Intervention:	During the concomitant use of INDOCIN SR and probenecid, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.	*Intervention:*	During the concomitant use of indomethacin extended-release capsules and probenecid, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in	*Intervention:*	During the concomitant use of indomethacin extended-release capsules and probenecid, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small

Effects on Laboratory Tests
Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or

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volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients. False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.	small increments. Effects on Laboratory Tests Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients. False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.		increments. Effects on Laboratory Tests Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients. False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.
8 USE IN SPECIFIC POPULATIONS	**8 USE IN SPECIFIC POPULATIONS**		**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy Risk Summary Use of NSAIDs, including INDOCIN SR, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of INDOCIN SR use between about 20 and 30 weeks of gestation, and avoid INDOCIN SR use at about 30 weeks of	**8.1 Pregnancy** Risk Summary Use of NSAIDs, including indomethacin extended-release capsules, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of indomethacin extended-		**8.1 Pregnancy** Risk Summary Use of NSAIDs, including indomethacin extended-release capsules, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of indomethacin extended-release capsules use

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gestation and later in pregnancy (*see Clinical Considerations, Data*). *Premature Closure of Fetal Ductus Arteriosus* Use of NSAIDS, including INDOCIN SR, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus. *Oligohydramnios/Neonatal Renal Impairment* Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies retarded fetal ossification was observed with administration of indomethacin to mice and rats during organogenesis at doses 0.1 and 0.2 times, respectively, the maximum recommended human dose (MRHD, 200 mg). In published studies in pregnant mice, indomethacin produced maternal toxicity and death, increased fetal resorptions, and fetal malformations at 0.1 times the MRHD. When rat and mice dams	release capsules use between about 20 and 30 weeks of gestation, and avoid indomethacin extended-release capsules use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*). *Premature Closure of Fetal Ductus Arteriosus* Use of NSAIDs, including indomethacin extended-release capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus. *Oligohydramnios/Neonatal Renal Impairment* Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies retarded fetal ossification was observed with administration of indomethacin to mice and rats during		between about 20 and 30 weeks of gestation, and avoid indomethacin extended-release capsules use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*). *Premature Closure of Fetal Ductus Arteriosus* Use of NSAIDs, including indomethacin extended-release capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus. *Oligohydramnios/Neonatal Renal Impairment* Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies retarded fetal ossification was observed with administration of indomethacin to mice and rats during organogenesis at doses 0.1 and 0.2 times, respectively, the maximum recommended human

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were dosed during the last three days of gestation, indomethacin produced neuronal necrosis in the offspring at 0.1 and 0.05 times the MRHD, respectively [see *Data*]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as indomethacin, resulted in increased pre-and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.	organogenesis at doses 0.1 and 0.2 times, respectively, the maximum recommended human dose (MRHD, 200 mg). In published studies in pregnant mice, indomethacin produced maternal toxicity and death, increased fetal resorptions, and fetal malformations at 0.1 times the MRHD. When rat and mice dams were dosed during the last three days of gestation, indomethacin produced neuronal necrosis in the offspring at 0.1 and 0.05 times the MRHD, respectively [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as indomethacin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general		dose (MRHD, 200 mg). In published studies in pregnant mice, indomethacin produced maternal toxicity and death, increased fetal resorptions, and fetal malformations at 0.1 times the MRHD. When rat and mice dams were dosed during the last three days of gestation, indomethacin produced neuronal necrosis in the offspring at 0.1 and 0.05 times the MRHD, respectively [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as indomethacin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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Clinical Considerations *Fetal/Neonatal Adverse Reactions* Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including INDOCIN SR, can cause premature closure of the fetal ductus arteriosus (*see Data*). Oligohydramnios/Neonatal Renal Impairment: If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If INDOCIN SR treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue INDOCIN SR and follow up according to clinical practice (*see Data*).	population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations *Fetal/Neonatal Adverse Reactions* Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including indomethacin extended-release capsules, can cause premature closure of the fetal ductus arteriosus (see Data). *Oligohydramnios/Neonatal Renal Impairment* If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If indomethacin extended-release capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue indomethacin extended-release		Clinical Considerations *Fetal/Neonatal Adverse Reactions* Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including indomethacin extended-release capsules, can cause premature closure of the fetal ductus arteriosus (see Data). *Oligohydramnios/Neonatal Renal Impairment* If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If indomethacin extended-release capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue indomethacin extended-release capsules and follow up according to clinical practice (see Data).

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	capsules and follow up according to clinical practice (see Data).		
Data	Data		Data
Human Data Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus. Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of	*Human Data* Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus. Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of		*Human Data* Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus. Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible.

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which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis. Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.	case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis. Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.		Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis. Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.
Animal data Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.1 times [mice] and 0.2 times [rats] the MRHD on a mg/m^2 basis, respectively) considered secondary to the	*Animal data* Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.1 times [mice] and 0.2 times [rats] the MRHD on a mg/m2 basis, respectively) considered secondary to		*Animal data* Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.1 times [mice] and 0.2 times [rats] the MRHD on a mg/m2 basis, respectively) considered secondary to the decreased average

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decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.1 to 0.4 times MRHD on a mg/m^2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. In rats and mice, maternal indomethacin administration of 4.0 mg/kg/day (0.2 times and 0.1 times the MRHD on a mg/m^2 basis) during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups (0.1 times and 0.05 times the MRHD on a mg/m^2 basis). Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.	the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.1 to 0.4 times MRHD on a mg/m2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. In rats and mice, maternal indomethacin administration of 4.0 mg/kg/day (0.2 times and 0.1 times the MRHD on a mg/m2 basis) during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups (0.1 times and 0.05 times the MRHD on a mg/m2 basis). Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.		fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.1 to 0.4 times MRHD on a mg/m2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. In rats and mice, maternal indomethacin administration of 4.0 mg/kg/day (0.2 times and 0.1 times the MRHD on a mg/m2 basis) during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups (0.1 times and 0.05 times the MRHD on a mg/m2 basis). Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.
8.2 Lactation Risk Summary	**8.2 Lactation** Risk Summary Based on available published clinical data, indomethacin may be present in human milk.		**8.2 Lactation** Risk Summary Based on available published clinical data, indomethacin may be present in human milk.

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Based on available published clinical data, indomethacin may be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INDOCIN SR and any potential adverse effects on the breastfed infant from the INDOCIN SR or from the underlying maternal condition. Data In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% of the maternal weight-adjusted dose. In another study indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The estimated infant dose of indomethacin from breast milk was less than 30 mcg/day or 4.5 mcg/ kg/day assuming breast milk intake of 150 mL/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3%	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for indomethacin extended-release capsules and any potential adverse effects on the breastfed infant from the indomethacin extended-release capsules or from the underlying maternal condition. Data In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% of the maternal weight- adjusted dose. In another study indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The estimated infant dose of indomethacin from breast milk was less than 30 mcg/day or 4.5 mcg/ kg/day assuming breast milk intake of 150 mL/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for		The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for indomethacin extended-release capsules and any potential adverse effects on the breastfed infant from the indomethacin extended-release capsules or from the underlying maternal condition. Data In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% of the maternal weight- adjusted dose. In another study indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The estimated infant dose of indomethacin from breast milk was less than 30 mcg/day or 4.5 mcg/ kg/day assuming breast milk intake of 150 mL/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of patent ductus arteriosus.

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of the neonatal dose for treatment of patent ductus arteriosus.	treatment of patent ductus arteriosus.		
8.3 Females and Males of Reproductive Potential Infertility *Females* Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including INDOCIN SR, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandinmediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including INDOCIN SR, in women who have difficulties conceiving or who are undergoing investigation of infertility.	**8.3 Females and Males of Reproductive Potential** Infertility *Females* Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including indomethacin extended-release capsules, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including indomethacin extended-release capsules, in women who have difficulties conceiving or who are undergoing investigation of infertility.		**8.3 Females and Males of Reproductive Potential** Infertility *Females* Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including indomethacin extended-release capsules, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including indomethacin extended-release capsules, in women who have difficulties conceiving or who are undergoing investigation of infertility.
8.4 Pediatric Use Safety and effectiveness in pediatric patients 14 years of age and younger has not been established.	**8.4 Pediatric Use**		**8.4 Pediatric Use**

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INDOCIN SR should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk. In experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with indomethacin immediate-release capsules, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of indomethacin immediate-release capsules. If a decision is made to use indomethacin for pediatric patients two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities. If indomethacin treatment is instituted, a suggested starting dose is 1-2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 3 mg/kg/day or 150-200 mg/day, whichever is less. Limited data are available to support the use of a maximum daily dosage of 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level	Safety and effectiveness in pediatric patients 14 years of age and younger has not been established. Indomethacin extended-release capsules should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk. In experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with indomethacin immediate-release capsules, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of indomethacin immediate-release capsules. If a decision is made to use indomethacin for pediatric patients two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities. If indomethacin treatment is instituted, a suggested starting dose is 1-2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 3 mg/kg/day or 150-200 mg/day, whichever is less. Limited data are available to support the use of a		Safety and effectiveness in pediatric patients 14 years of age and younger has not been established. Indomethacin extended-release capsules should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk. In experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with indomethacin immediate-release capsules, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of indomethacin immediate-release capsules. If a decision is made to use indomethacin for pediatric patients two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities. If indomethacin treatment is instituted, a suggested starting dose is 1-2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 3 mg/kg/day or 150-200 mg/day, whichever is less. Limited data are available to support the use of a

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required to control symptoms, or the drug should be discontinued.	maximum daily dosage of 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.		maximum daily dosage of 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.
8.5 Geriatric Use Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)*]. Indomethacin may cause confusion or rarely, psychosis [*see Adverse Reactions (6.1)*]*;* physicians should remain alert to the possibility of such adverse effects in the elderly Indomethacin and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use caution in this patient	**8.5 Geriatric Use** Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)*]. Indomethacin may cause confusion or rarely, psychosis [*see Adverse Reactions (6.1)*]; physicians should remain alert to the possibility of such adverse effects in the elderly. Indomethacin and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use		**8.5 Geriatric Use** Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)*]. Indomethacin may cause confusion or rarely, psychosis [*see Adverse Reactions (6.1)*]; physicians should remain alert to the possibility of such adverse effects in the elderly. Indomethacin and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use caution in this patient population, and it may be useful to monitor renal function [*see Clinical Pharmacology (12.3)*]

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population, and it may be useful to monitor renal function [see *Clinical Pharmacology (12.3*)]	caution in this patient population, and it may be useful to monitor renal function [*see Clinical Pharmacology (12.3)*]		
10 OVERDOSAGE Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*]. Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding. For additional information about overdosage treatment contact a poison control center (1800-222-1222).	**10 OVERDOSAGE** Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*]. Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.		**10 OVERDOSAGE** Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*]. Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding. For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

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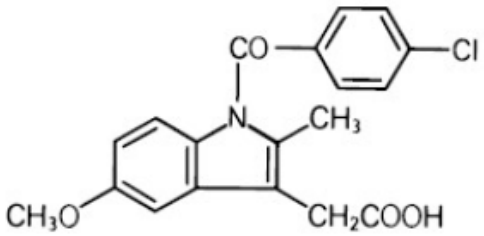
	For additional information about overdosage treatment contact a poison control center (1-800-222-1222).		
11 DESCRIPTION	**11 DESCRIPTION**		**11 DESCRIPTION**
INDOCIN SR (indomethacin) extended-release capsules are nonsteroidal anti-inflammatory drugs, available as capsules containing 75 mg of indomethacin, administered for oral use. The chemical name is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid. The molecular weight is 357.8. Its molecular formula is C19H16ClNO4 , and it has the following chemical structure.	Indomethacin extended-release capsules are nonsteroidal anti-inflammatory drugs, available as capsules containing 75 mg of indomethacin, administered for oral use. The chemical name is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The molecular weight is 357.8. Its molecular formula is $C_{19}H_{16}ClNO_4$, and it has the following chemical structure.		Indomethacin extended-release capsules are nonsteroidal anti-inflammatory drugs, available as capsules containing 75 mg of indomethacin, administered for oral use. The chemical name is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The molecular weight is 357.8. Its molecular formula is $C_{19}H_{16}ClNO_4$, and it has the following chemical structure.
			
Indomethacin is a white to yellow crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali.	Indomethacin is a pale yellow to yellow-tan crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol. It has a		Indomethacin is a pale yellow to yellow-tan crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol. It has a pKa

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	pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali.		of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali.
Inactive ingredients: ammonio methacrylate copolymer, black iron oxide (10 and 40 mg capsules only), gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide (10 and 40 mg capsules only), sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10, 30, and 40 mg capsules only). The inactive ingredients in INDOCIN SR Capsules, 75 mg include: cellulose, confectioner's sugar, FD&C Blue 1, FD&C Blue 2, FD&C Red 3, gelatin, hydroxypropyl methylcellulose, magnesium stearate, polyvinyl acetate-crotonic acid copolymer, starch, and titanium dioxide.	The inactive ingredients in Indomethacin Extended-Release Capsules, 75 mg include: corn starch, D&C Yellow # 10, gelatin, mannitol, povidone, sucrose, talc, and titanium dioxide.		The inactive ingredients in Indomethacin Extended-Release Capsules, 75 mg include: corn starch, D&C Yellow # 10, gelatin, mannitol, povidone, sucrose, talc, and titanium dioxide.
	This product meets USP Drug Release Test 2 Specifications.		This product meets USP Drug Release Test 2 Specifications.
12 CLINICAL PHARMACOLOGY	**12 CLINICAL PHARMACOLOGY**		**12 CLINICAL PHARMACOLOGY**
12.1Mechanism of Action Indomethacin has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of INDOCIN SR, like that of other NSAIDs, is not completely understood but	**12.1 Mechanism of Action** Indomethacin has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of indomethacin extended-release capsules, like that of other NSAIDs, is not completely understood but		**12.1 Mechanism of Action** Indomethacin has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of indomethacin extended-release capsules, like that of other NSAIDs, is not completely understood but

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involves inhibition of cyclooxygenase (COX-1 and COX-2). Indomethacin is a potent inhibitor of prostaglandin synthesis in vitro. Indomethacin concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	involves inhibition of cyclooxygenase (COX-1 and COX-2). Indomethacin is a potent inhibitor of prostaglandin synthesis in vitro. Indomethacin concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.		involves inhibition of cyclooxygenase (COX-1 and COX-2). Indomethacin is a potent inhibitor of prostaglandin synthesis in vitro. Indomethacin concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.
12.3Pharmacokinetics Absorption Following single oral doses of indomethacin immediate-release capsules 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin immediate-release capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of INDOCIN oral suspension was found to be bioequivalent to a 50 mg INDOCIN Capsule when each was administered with food. With a typical	**12.3 Pharmacokinetics** Absorption Following single oral doses of indomethacin immediate-release capsules 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin immediate-release capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of indomethacin oral suspension was found to be bioequivalent to a 50 mg indomethacin capsule when each was		**12.3 Pharmacokinetics** Absorption Following single oral doses of indomethacin immediate-release capsules 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin immediate-release capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of indomethacin oral suspension was found to be bioequivalent to a 50 mg indomethacin capsule when each was

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therapeutic regimen of 25 or 50 mg three times a day, the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose. INDOCIN SR 75 mg are designed to release 25 mg of the drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24-hour period, the cumulative amount and time-course of indomethacin absorption from a single indomethacin extended-release capsule are comparable to those of 3 doses of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin immediate-release capsules 25 mg given at 0, 6 and 12 hours daily. However, there was a significant difference in indomethacin	administered with food. With a typical therapeutic regimen of 25 or 50 mg three times a day, the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose. Indomethacin extended-release capsules 75 mg are designed to release 25 mg of the drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24-hour period, the cumulative amount and time-course of indomethacin absorption from a single indomethacin extended-release capsule are comparable to those of 3 doses of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals. Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin immediate-release capsules 25 mg given at 0, 6 and 12 hours daily. However,		administered with food. With a typical therapeutic regimen of 25 or 50 mg three times a day, the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose. Indomethacin extended-release capsules 75 mg are designed to release 25 mg of the drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24-hour period, the cumulative amount and time-course of indomethacin absorption from a single indomethacin extended-release capsule are comparable to those of 3 doses of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals. Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin immediate-release capsules given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin immediate-release capsules 25 mg given at 0, 6 and 12 hours daily. However, there was a significant difference in

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plasma levels between the two dosage regimens especially after 12 hours.	there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.		indomethacin plasma levels between the two dosage regimens especially after 12 hours.
Distribution Indomethacin is highly bound to protein in plasma (about 99%) over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta, and appears in breast milk.	Distribution Indomethacin is highly bound to protein in plasma (about 99%) over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta, and appears in breast milk.		Distribution Indomethacin is highly bound to protein in plasma (about 99%) over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta, and appears in breast milk.
Elimination	Elimination		Elimination
Metabolism Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of each metabolite and of indomethacin are formed.	*Metabolism* Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of each metabolite and of indomethacin are formed.		*Metabolism* Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of each metabolite and of indomethacin are formed.
Excretion Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 60% of an oral dose is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5%	*Excretion* Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 60% of an oral dose is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin). The mean half-life of		*Excretion* Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 60% of an oral dose is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5%

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as indomethacin). The mean half-life of indomethacin is estimated to be about 4.5 hours.	indomethacin is estimated to be about 4.5 hours.		as indomethacin). The mean half-life of indomethacin is estimated to be about 4.5 hours.
Specific Populations	Specific Populations		Specific Populations
Pediatric: The pharmacokinetics of INDOCIN SR has not been investigated in pediatric patients.	*Pediatric*: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in pediatric patients.		*Pediatric*: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in pediatric patients.
Race: Pharmacokinetic differences due to race have not been identified.	*Race*: Pharmacokinetic differences due to race have not been identified.		*Race*: Pharmacokinetic differences due to race have not been identified.
Hepatic Impairment: The pharmacokinetics of INDOCIN SR has not been investigated in patients with hepatic impairment.	*Hepatic Impairment*: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in patients with hepatic impairment.		*Hepatic Impairment*: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in patients with hepatic impairment.
Renal Impairment: The pharmacokinetics of INDOCIN SR has not been investigated in patients with renal impairment [see Warnings and Precautions (5.6)].	*Renal Impairment*: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in patients with renal impairment [*see Warnings and Precautions (5.6)*].		*Renal Impairment*: The pharmacokinetics of indomethacin extended-release capsules has not been investigated in patients with renal impairment [*see Warnings and Precautions (5.6)*].
Drug Interaction Studies	Drug Interaction Studies		Drug Interaction Studies
Aspirin: In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20% [*see Drug Interactions (7)]*.	*Aspirin:* In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin		*Aspirin:* In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood

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When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].	blood levels approximately 20% [*see Drug Interactions (7)*]. When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].		levels approximately 20% [*see Drug Interactions (7)*]. When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].
Diflunisal: In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin [*see Drug Interactions (7)*].	*Diflunisal:* In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin [*see Drug Interactions (7)*].		*Diflunisal:* In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin [*see Drug Interactions (7)*].
13 NONCLINICAL TOXICOLOGY	**13 NONCLINICAL TOXICOLOGY**		**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility <u>Carcinogenesis</u> In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.05 times the MRHD on a mg/m^2 basis), indomethacin had no tumorigenic effect. Indomethacin produced no	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>Carcinogenesis</u> In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.05 times the MRHD on a mg/m2 basis), indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat		**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>Carcinogenesis</u> In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.05 times the MRHD on a mg/m2 basis), indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat

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neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73 to 110 weeks) and the mouse (dosing period 62 to 88 weeks) at doses up to 1.5 mg/kg/day (0.04 times [mice] and 0.07 times [rats] the MRHD on a mg/m^2 basis, respectively). Mutagenesis Indomethacin did not have any mutagenic effect in in vitro bacterial tests and a series of in vivo tests including the host-mediated assay, sex-linked recessive lethals in Drosophila, and the micronucleus test in mice. Impairment of Fertility Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.01 times the MRHD on a mg/m^2 basis) or a two litter reproduction study in rats (0.02 times the MRHD on a mg/m^2 basis).	(dosing period 73 to 110 weeks) and the mouse (dosing period 62 to 88 weeks) at doses up to 1.5 mg/kg/day (0.04 times [mice] and 0.07 times [rats] the MRHD on a mg/m2 basis, respectively). Mutagenesis Indomethacin did not have any mutagenic effect in in vitro bacterial tests and a series of in vivo tests including the host-mediated assay, sex-linked recessive lethals in Drosophila, and the micronucleus test in mice. Impairment of Fertility Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.01 times the MRHD on a mg/m2 basis) or a two litter reproduction study in rats (0.02 times the MRHD on a mg/m^2 basis).		(dosing period 73 to 110 weeks) and the mouse (dosing period 62 to 88 weeks) at doses up to 1.5 mg/kg/day (0.04 times [mice] and 0.07 times [rats] the MRHD on a mg/m2 basis, respectively). Mutagenesis Indomethacin did not have any mutagenic effect in in vitro bacterial tests and a series of in vivo tests including the host-mediated assay, sex-linked recessive lethals in Drosophila, and the micronucleus test in mice. Impairment of Fertility Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.01 times the MRHD on a mg/m2 basis) or a two litter reproduction study in rats (0.02 times the MRHD on a mg/m^2 basis).
14 CLINICAL STUDIES	**14 CLINICAL STUDIES**		**14 CLINICAL STUDIES**
Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.	Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.		Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

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INDOCIN SR affords relief of symptoms; it does not alter the progressive course of the underlying disease. INDOCIN SR suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength. INDOCIN SR may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.	Indomethacin extended-release capsules affords relief of symptoms; it does not alter the progressive course of the underlying disease. Indomethacin extended-release capsules suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength. Indomethacin extended-release capsules may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.		Indomethacin extended-release capsules affords relief of symptoms; it does not alter the progressive course of the underlying disease. Indomethacin extended-release capsules suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength. Indomethacin extended-release capsules may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.
16 HOW SUPPLIED/STORAGE AND HANDLING INDOCIN SR (indomethacin) extended-release capsules, 75 mg each, are opaque blue cap and clear	**16 HOW SUPPLIED/STORAGE AND HANDLING** Indomethacin extended-release capsules, 75 mg each, are supplied as yellow opaque cap and natural body with black imprint "K 16"		**16 HOW SUPPLIED/STORAGE AND HANDLING** Indomethacin extended-release capsules, 75 mg each, are supplied as yellow opaque cap and

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body, containing a mixture of blue and white pellets. NDC 60951-774-60: unit of use bottles of 60 NDC 60951-774-70: bottles of 100 <u>Storage</u> Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	on both cap and body, filled with white pellets. Bottles of 30 capsules, NDC 10702-016-03 Bottles of 60 capsules, NDC 10702-016-06 Bottles of 90 capsules, NDC 10702-016-09 Bottles of 100 capsules, NDC 10702-016-01 Bottles of 500 capsules, NDC 10702-016-50 Bottles of 1000 capsules, NDC 10702-016-10 Storage Store at room temperature 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.		natural body with black imprint "K 16" on both cap and body, filled with white pellets. Bottles of 30 capsules, NDC 10702-016-03 Bottles of 60 capsules, NDC 10702-016-06 Bottles of 90 capsules, NDC 10702-016-09 Bottles of 100 capsules, NDC 10702-016-01 Bottles of 500 capsules, NDC 10702-016-50 Bottles of 1000 capsules, NDC 10702-016-10 Storage Store at room temperature 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
17 PATIENT COUNSELING INFORMATION	**17 PATIENT COUNSELING INFORMATION**		**17 PATIENT COUNSELING INFORMATION**
Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with	Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with indomethacin extended-release		Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with

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INDOCIN SR and periodically during the course of ongoing therapy.	capsules and periodically during the course of ongoing therapy.		indomethacin extended-release capsules and periodically during the course of ongoing therapy.
Cardiovascular Thrombotic Events Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see Warnings and Precautions (5.1)].	Cardiovascular Thrombotic Events Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].		Cardiovascular Thrombotic Events Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].
Gastrointestinal Bleeding, Ulceration, and Perforation Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].	Gastrointestinal Bleeding, Ulceration, and Perforation Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].		Gastrointestinal Bleeding, Ulceration, and Perforation Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].
Hepatotoxicity Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy,	Hepatotoxicity Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice,		Hepatotoxicity Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant

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pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop INDOCIN SR and seek immediate medical therapy [see Warnings and Precautions (5.3)].	right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop indomethacin extended-release capsules and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].		tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop indomethacin extended-release capsules and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].
Heart Failure and Edema Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].	Heart Failure and Edema Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].		Heart Failure and Edema Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].
Anaphylactic Reactions Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7)].	Anaphylactic Reactions Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].		Anaphylactic Reactions Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].
Serious Skin Reactions, including DRESS Advise patients to stop taking INDOCIN SR immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9, 5.10)].	Serious Skin Reactions, including DRESS Advise patients to stop taking indomethacin extended-release capsules immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10*].		Serious Skin Reactions, including DRESS Advise patients to stop taking indomethacin extended-release capsules immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10*].

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Female Fertility Advise females of reproductive potential who desire pregnancy that NSAIDs, including INDOCIN SR, may be associated with a reversible delay in ovulation [see Use in Specific Populations (8.3)].	Female Fertility Advise females of reproductive potential who desire pregnancy that NSAIDs, including indomethacin extended-release capsules, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].		Female Fertility Advise females of reproductive potential who desire pregnancy that NSAIDs, including indomethacin extended-release capsules, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].
Fetal Toxicity Inform pregnant women to avoid use of INDOCIN SR and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with INDOCIN SR is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)].	Fetal Toxicity Inform pregnant women to avoid use of indomethacin extended-release capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with indomethacin extended-release capsules is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].		Fetal Toxicity Inform pregnant women to avoid use of indomethacin extended-release capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with indomethacin extended-release capsules is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].
Avoid Concomitant Use of NSAIDs Inform patients that the concomitant use of INDOCIN SR with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and	Avoid Concomitant Use of NSAIDs Inform patients that the concomitant use of indomethacin extended-release capsules with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the		Avoid Concomitant Use of NSAIDs Inform patients that the concomitant use of indomethacin extended-release capsules with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of

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little or no increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7)]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.	increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.		gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.
Use of NSAIDs and Low-Dose Aspirin Inform patients not to use low-dose aspirin concomitantly with INDOCIN SR until they talk to their healthcare provider [*see Drug Interactions (7)*].	Use of NSAIDs and Low-Dose Aspirin Inform patients not to use low-dose aspirin concomitantly with indomethacin until they talk to their healthcare provider [*see Drug Interactions (7)*].		Use of NSAIDs and Low-Dose Aspirin Inform patients not to use low-dose aspirin concomitantly with indomethacin until they talk to their healthcare provider [*see Drug Interactions (7)*].
Manufactured for and Distributed by: Zyla Life Sciences US, Inc. Wayne, PA 19087	Manufactured by: KVK-TECH INC. 110 Terry Drive Newtown, PA 18940 KVK | TECH Item ID # 6030/08 Manufacturer's Code: 10702 04/2021	2	Manufactured by: KVK-TECH INC. 110 Terry Drive Newtown, PA 18940 KVK | TECH Item ID # 6030/09 Manufacturer's Code: 10702 07/2024
MEDICATION GUIDE	**MEDICATION GUIDE**		**MEDICATION GUIDE**

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Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	**Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**		**Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**
What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)? **NSAIDs can cause serious side effects, including:** • **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase: o with increasing doses of NSAIDs o with longer use of NSAIDs **Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."** **Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.** • **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:** o anytime during use o without warning symptoms o that may cause death **The risk of getting an ulcer or bleeding increases with:** o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"	**What is the most important information I should know about medicines called Nonsteroidal Anti- inflammatory Drugs (NSAIDs)?** **NSAIDs can cause serious side effects, including:** • **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase: o with increasing doses of NSAIDs o with longer use of NSAIDs **Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."** **Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.** • **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:** o anytime during use o without warning symptoms o that may cause death **The risk of getting an ulcer or bleeding**		**What is the most important information I should know about medicines called Nonsteroidal Anti- inflammatory Drugs (NSAIDs)?** **NSAIDs can cause serious side effects, including:** • **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase: o with increasing doses of NSAIDs o with longer use of NSAIDs **Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."** **Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.** • **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:** o anytime during use o without warning symptoms o that may cause death **The risk of getting an ulcer or bleeding increases with:** o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs

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o increasing doses of NSAIDs o longer use of NSAIDs o smoking o drinking alcohol o older age o poor health o advanced liver disease o bleeding problems **NSAIDs should only be used:** o exactly as prescribed o at the lowest dose possible for your treatment o for the shortest time needed	**increases with:** o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs" o increasing doses of NSAIDs o longer use of NSAIDs o smoking o drinking alcohol o older age o poor health o advanced liver disease o bleeding problems **NSAIDs should only be used:** o exactly as prescribed o at the lowest dose possible for your treatment o for the shortest time needed		o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs" o increasing doses of NSAIDs o longer use of NSAIDs o smoking o drinking alcohol o older age o poor health o advanced liver disease o bleeding problems **NSAIDs should only be used:** o exactly as prescribed o at the lowest dose possible for your treatment o for the shortest time needed
What are NSAIDs? NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.	**What are NSAIDs?** NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.		**What are NSAIDs?** NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.
Who should not take NSAIDs? **Do not take NSAIDs:**	**Who should not take NSAIDs?**		**Who should not take NSAIDs?**

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• if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs. • right before or after heart bypass surgery.	**Do not take NSAIDs:** • if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs. • right before or after heart bypass surgery.		**Do not take NSAIDs:** • if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs. • right before or after heart bypass surgery.
Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you: • have liver or kidney problems • have high blood pressure • have asthma • are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.** • are breastfeeding or plan to breast feed. **Tell your healthcare provider about all of the medicines you take, including prescription or over-the- counter medicines, vitamins or herbal**	**Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:** • have liver or kidney problems • have high blood pressure • have asthma • are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.** • are breastfeeding or plan to breast feed. **Tell your healthcare provider about all of**		**Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:** • have liver or kidney problems • have high blood pressure • have asthma • are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.** • are breastfeeding or plan to breast feed. **Tell your healthcare provider about all of the medicines you take, including prescription or over-the- counter medicines, vitamins or herbal**

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supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**	**the medicines you take, including prescription or over-the- counter medicines, vitamins or herbal supplements.** NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**		**supplements.** NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**
What are the possible side effects of NSAIDs? **NSAIDs can cause serious side effects, including:** **See "What is the most important information I should know about medicines called Nonsteroidal Anti- inflammatory Drugs (NSAIDs)?"** • new or worse high blood pressure • heart failure • liver problems including liver failure • kidney problems including kidney failure • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness. **Get emergency help right away if you get any of the following symptoms:** • shortness of breath or trouble breathing • chest pain	**What are the possible side effects of NSAIDs?** **NSAIDs can cause serious side effects, including:** **See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"** **inflammatory Drugs (NSAIDs)?"** • new or worse high blood pressure • heart failure • liver problems including liver failure • kidney problems including kidney failure • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness. **Get emergency help right away if you get any of the following**		**What are the possible side effects of NSAIDs?** **NSAIDs can cause serious side effects, including:** **See "What is the most important information I should know about medicines called Nonsteroidal Anti- inflammatory Drugs (NSAIDs)?"** **inflammatory Drugs (NSAIDs)?"** • new or worse high blood pressure • heart failure • liver problems including liver failure • kidney problems including kidney failure • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness. **Get emergency help right away if you get any of the following symptoms:** • shortness of breath or trouble breathing • chest pain

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• weakness in one part or side of your body • slurred speech • swelling of the face or throat **Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:** • nausea • more tired or weaker than usual • diarrhea • itching • your skin or eyes look yellow • indigestion or stomach pain • flu-like symptoms • vomit blood • there is blood in your bowel movement or it is black and sticky like tar • unusual weight gain • skin rash or blisters with fever • swelling of the arms, legs, hands and feet **If you take too much of your NSAID, call your healthcare provider or get medical help right away.** These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.	**symptoms:** • shortness of breath or trouble breathing • chest pain • weakness in one part or side of your body • slurred speech • swelling of the face or throat **Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:** • nausea • more tired or weaker than usual • diarrhea • itching • your skin or eyes look yellow • indigestion or stomach pain • flu-like symptoms • vomit blood • there is blood in your bowel movement or it is black and sticky like tar • unusual weight gain • skin rash or blisters with fever • swelling of the arms, legs, hands and feet **If you take too much of your NSAID, call your healthcare provider or get medical help right away.** These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to		• weakness in one part or side of your body • slurred speech • swelling of the face or throat **Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:** • nausea • more tired or weaker than usual • diarrhea • itching • your skin or eyes look yellow • indigestion or stomach pain • flu-like symptoms • vomit blood • there is blood in your bowel movement or it is black and sticky like tar • unusual weight gain • skin rash or blisters with fever • swelling of the arms, legs, hands and feet **If you take too much of your NSAID, call your healthcare provider or get medical help right away.** These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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	FDA at 1-800-FDA-1088.		
Other information about NSAIDs • Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines. • Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.	**Other information about NSAIDs** • Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines. • Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.		**Other information about NSAIDs** • Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines. • Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.
General information about the safe and effective use of NSAIDs Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.	**General information about the safe and effective use of NSAIDs** Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.		**General information about the safe and effective use of NSAIDs** Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.
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For more information, go to www.zyla.com or call 1-877-757-0676	110 Terry Drive Newtown PA 18940 For more information, go to www.kvktech.com or call our customer service at 1-800-862-3895		110 Terry Drive Newtown PA 18940 For more information, go to www.kvktech.com or call our customer service at 1-800-862-3895
This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued or Revised: 04/2021	This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued or Revised: April 2021	2	This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued or Revised: July 2024

Differences and Annotation:

1	Information is Updated/Edited/Deleted as per Safety Labelling Change Notification Letter from FDA dated 07/10/2024.
2	Item ID, Revision and date are revised to match with current revision and practice.