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# Drug INDEX

Passi HealthCom

SPECIAL SUPPLEMENT ON ONCOLOGY

Oncology

is the study of cancer. A  
called an on



Passi HealthCom

# Get...CET...GO! with



## High Performance Pain Relief



### Multimodal Action

- Exhibits Central Action by binding to  $\mu$  opioid receptors<sup>1,2</sup>
- Inhibits Central Sensitization<sup>3</sup>
- Exhibits Peripheral Action<sup>4</sup>

### Organ Friendly

#### Well tolerated in both young adults and elderly<sup>5</sup>



Cardio Friendly



GI Friendly



Renal Friendly<sup>6,7</sup>

## Rapid onset of action – in 17 minutes<sup>8</sup>

Ref.: 1. Bjorkman R et al. Pain. 1994;57:259-264    2. Muth-Selbach US et al. Anesthesiology. 1999; 91:231-9    3. M.Bianchi et al. Anesthesia & Analgesia. 2007; Vol. 104 (4): 949-954    4. Stein C et al. Nat Med. 2003 Aug;9(8):1003-8    5. O. Mejjad et al. SALZA study. May 2011; Vol. 27(5): 1013-1020    6. S. Schug. Therapeutics and Clinical Risk Management. 2007; 3(5):717-723    7. S.A Schug. Clin Rheumatol. 2006; 25(Suppl 1):S156-521    8. Sawaddiruk P. Drugs Today. 2011 Oct;47(10): 763-72

Additional information available on request.

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

Acetaminophen & Tramadol Hydrochloride Tablets USP

**ULTRACET® SEMI**

**Composition:** Ultracet® Ultracet® semi is available as tablets for oral administration containing 37.5/18.75 mg tramadol hydrochloride and 325/162.5 mg acetaminophen. **Indication:** It is indicated for the management of severe acute pain. **Posology and method of administration:** For adults and children over 16 years—Ultracet® Ultracet® semi should not be used for more than 5 days when used for the treatment of severe acute pain. The maximum single dose of Ultracet® Ultracet® semi tablets is 2 tablets every 4 to 6 hours. **Contraindications:** Ultracet® Ultracet® semi should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or its opioids. It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. **Special warnings and special precautions for use:** Seizures have been reported in patients receiving tramadol within the recommended dosage range. Risk of convulsions may also increase in patients with epilepsy, those with a history of seizure, or in patients with a recognized risk for seizure. In tramadol overdose, Naloxone administration may increase the risk of seizure. Patients with a history of anapylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive Ultracet® Ultracet® semi. Administer Ultracet® Ultracet® semi cautiously in patients at risk for respiratory depression in patients with increased intracranial pressure or head injury and in patients taking monoamine oxidase inhibitors. After discontinuing Ultracet® Ultracet® semi, and/or increased dosing, and/or increased monitoring for signs of tramadol overdose, such as respiratory depression, as recommended in patients known to be at risk for respiratory depression, should be discontinued if there is evidence of respiratory depression. Ultracet® Ultracet® semi should not be co-administered with other tramadol or acetaminophen-containing products. **Interactions with other medicinal products and other forms of interaction:** Patients taking carbamazepine may have a significantly reduced analgesic effect from the tramadol component of Ultracet® Ultracet® semi. Concomitant administration of quinidine and tramadol results in increased concentrations of tramadol. As medically appropriate, periodic evaluation of prothrombin time should be performed when Ultracet® Ultracet® semi and these agents are administered concurrently due to reports of increased INR in some patients. **Pregnancy and lactation:** Safe use in pregnancy has not been established. Ultracet® Ultracet® semi is not recommended for nursing mothers. **Undesirable effects:** The most frequently reported events were in the central nervous system and gastrointestinal system which include nausea, dizziness, and somnolence. **Overdose:** The initial symptoms of tramadol overdose may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose may include gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis. A single or multiple overdose with Ultracet® Ultracet® semi may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.

**SCHEDULE H1 WARNING:** It is dangerous to take this preparation except in accordance with the medical advice. Not to be sold by retail without the prescription of a Registered Medical Practitioner

**Warning:** Taking more than the recommended daily dose, may cause serious liver damage or allergic reactions (e.g. swelling of the face, mouth and throat, difficulty in breathing, itching or rash). In case of overdose, get medical help right away. Quick medical attention is critical even if you do not notice any signs or symptoms.

**Made in India by:**

Johnson & Johnson Private Limited, L.B.S. Marg, Mulund (West), Mumbai 400060

\* Registered trademark of Johnson & Johnson, USA

For complete product information, please contact Johnson & Johnson Private Limited,

L.B.S. Marg, Mulund (West), Mumbai - 400 080. Phone: 022-2564441,

Version: CDD 23 Sep 2015

Johnson & Johnson Private Limited (formerly Johnson & Johnson Limited)

with corporate identity number U33110MH195PTC01928 has its registered office at

L.B.S. Marg, Mulund (West), Mumbai - 400 080. Phone: 022-2564441,

website: www.jnjindia.com.

# In the management of **chronic pain** and **intractable pain** requiring opioid analgesia

# Durogesic®

fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

72 HOUR PAIN RELIEF



Round the clock –  
continuous  
drug delivery<sup>1</sup>



Improved  
convenience and  
patient compliance<sup>1</sup>



Better  
tolerability<sup>#,2,3</sup>

# In comparison with morphine.

References: 1. Lee JH, Yun HC, Lee GJ et al. The Impact of Fentanyl Matrix on Pain and Function in Spinal Disorder-Related Chronic Pain: An Open Label Trial in Korea. Asian Spine Journal 2011; 5(2): 91-99. 2. Berliner

MN, Giesecke T, Borhovd KLD. Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. Clin J Pain. 2007 Jul-Aug;23(6):530-4. 3. Choquette D, et al Transdermal fentanyl improves pain control and functionality in patients with osteoarthritis: an open-label Canadian trial. Clin Rheumatol 2008; 27(5): 587-595.

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

NRx, O-Tans Fentanyl Transdermal Patch. **Durogesic® COMPOSITION:** Durogesic® transdermal patch is designed to deliver 12.5 mcg/hr, 25 mcg/hr, 50 mcg/hr of Fentanyl. **Pharmaceutical form:** Transdermal patch providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. **Therapeutic indications:** Durogesic® is indicated in the management of chronic pain and intractable pain requiring opioid analgesia. **POSSOLOGY AND METHOD OF ADMINISTRATION:** Durogesic® doses should be applied to the skin at the recommended starting dose and should be assessed at 24-hour intervals after application. For conversion from oral or parenteral opioid to Durogesic®, refer to label. **Opioid-tolerant Patients:** For conversion from oral or parenteral opioid to Durogesic®, refer to label. **Opioid-naïve Patients:** Durogesic® should be titrated with low doses of immediate-release opioids to attain equianalgesic dosage relative to Durogesic® with a release rate of 25 mcg/hr. The patients can then be converted to Durogesic® 25 mcg/hr. In both the cases, the dosage may subsequently be titrated upwards or downwards. If required, in increments of either 12 or 25 mcg/hr, to achieve the lowest appropriate dose of Durogesic® depending on response and supplementary analgesic requirements. The Durogesic® patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained. For more details on Dosage Titration and Maintenance Therapy kindly refer to Package Insert. If discontinuation of Durogesic® is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly in order to prevent withdrawal symptoms. **CONTRAINDICATIONS:** Durogesic® is contraindicated in patients with known hypersensitivity to fentanyl or to the adhesives present in the patch. Also, it is contraindicated for the management of acute or postoperative pain because there is no opportunity for dose titration during short-term use and also serious or life-threatening hypotension could result. **SPECIFIC WARNINGS AND SPECIFIC PRECAUTIONS FOR USE:** Patients who have experienced SAE's should be monitored for atleast 24 hours after Durogesic® removal. Durogesic® should be kept out of reach of children before and after use. A patient who has overdosed or delayed any treatment should be seen. Some patients may experience transient respiratory depression in Durogesic® and should be treated in the same way as for Dose-related respiratory depression. The incidence of respiratory depression increases as the Durogesic® dose is increased. Durogesic® may have severe adverse effects in patients with chronic obstructive or other pulmonary disease such as decrease respiratory drive and increase airway resistance. Abuse or intentional misuse of Durogesic® may result in overdose and/or death. Durogesic® should be used with caution in patients who may be particularly susceptible to the intracardiac effects of CO<sub>2</sub> retention and in those with brain tumors. Fentanyl may produce bradycardia and should be administered with caution to patients with bradycardia. Patients with hepatic or renal impairment should be observed carefully for signs of fentanyl toxicity and the dose of Durogesic® reduced if necessary. The dose of Durogesic® should be monitored in patients with fever. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients receiving Durogesic® and CYP3A4 inhibitors should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted. In case of Accidental Exposure by Patch Transfer, the transferred patch must be removed immediately from the skin of non-patch wearer in order to avoid opioid overdose for the nonpatch wearer. Elderly patients should be observed for signs of fentanyl toxicity and the dose reduced if necessary. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with Durogesic® should be stopped. Caution is advised when Durogesic® is coadministered with drugs that affect the serotonergic neurotransmitter systems. A potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-Uptake Inhibitors (SSRIs) and Serotonin/Norepinephrine Re-Uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose. Discontinuation of Durogesic® should be considered if serotonin syndrome is suspected. If serotonin syndrome is present or suspected, discontinuation of Durogesic® should be considered. Interaction with other medicinal products and other forms of interaction: The concomitant use of other CNS depressants may produce additive depressant effects, hypotension, hypotension and profound sedation, coma or death may occur. Careful monitoring is required in case of concomitant administration with CYP3A4 inducers, since it could result in decreased therapeutic effect. Durogesic® is not recommended concomitantly with Monoamine Oxidase Inhibitors (MAOIs). After Durogesic® should not be used within 14 days after discontinuation of treatment with MAOIs. **PREGNANCY AND LACTATION:** Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Durogesic® during pregnancy hence Durogesic® should not be used during pregnancy unless clearly necessary. Use of Durogesic® during childbirth is not recommended. Durogesic® is not recommended for use in nursing women. Effects on ability to drive and use machines: Durogesic® may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Undesirable effects: Often reported ones are somnolence, insomnia, dizziness, nausea, vomiting, constipation, fatigue, diarrhea, pyrexia etc. OVERDOSE: The most common effect found due to overdose is respiratory depression. For management of non-cardiovascular respiratory depressions include oxygen therapy. If the patient is unconscious, follow-up administration of a specific opioid antagonist such as naloxone should be carried out. If severe or persistent hypotension occurs, hypotension should be considered, and the condition should be managed with appropriate parenteral fluid therapy. **WARNING:** To be sold by retail on the prescription of a Registered Medical Practitioner only. \* Registered Trademark of Johnson & Johnson, U.S.A. For complete prescribing information, please contact Johnson & Johnson Private Limited, Arena Space, Behind Majas Bus Depot, Off J. V. Link Road, Jogleswari (East), Mumbai 400090. **Version:** 24 Jul 2013 **For complete prescribing information, please contact:** Johnson & Johnson Private Limited, Arena Space, Behind Majas Depot, Off J. V. Link Road, Jogleswari (E), Mumbai 400060. **Johnson & Johnson Private Limited (formerly Johnson & Johnson Limited) with corporate identity number U33110MH1957P7C019298 has its registered office at LBS Marg Mulund (West) Mumbai - 400 080. Phone: 022-2564441. website: www.jnjindia.com**

Additional information available on request

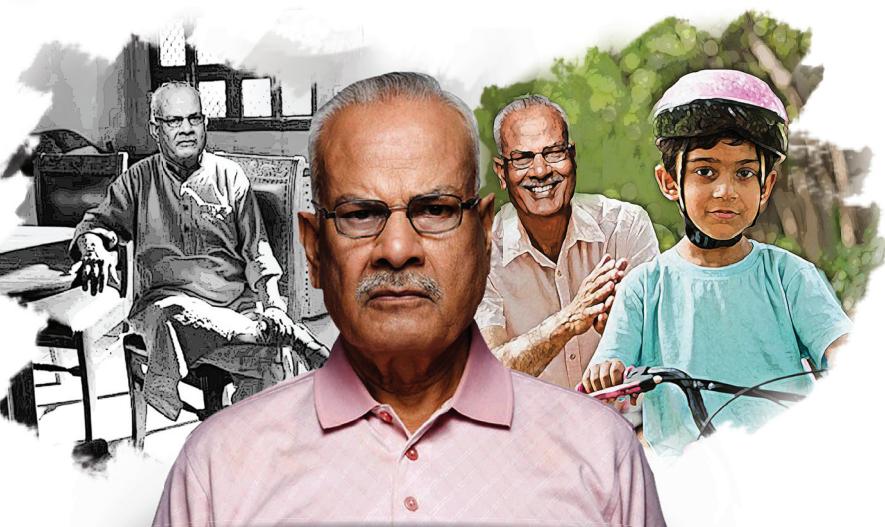
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PHARMACEUTICAL COMPANIES OF  
Johnson & Johnson

# LET HAPPINESS TAKE PRECEDENCE IN YOUR PATIENT'S LIFE



Rx In Peripheral Neuropathy  
**PRELOGIC™**  
Pregabalin 75mg + Methylcobalamin 750mcg  
The Logical Way

99.9% pure high affinity S enantiomer Pregabalin\*



\* Data on file

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Pregabalin and Methylcobalamin capsules

PRELOGIC

Composition: Each hard gelatin capsule contains pregabalin IP 75 mg and methylcobalamin 750 mcg. Indication: For the treatment of peripheral neuropathy. Dosage and administration: As directed by the physician. Contraindication: It is contraindicated in patients with known hypersensitivity to any component of the formulation. Warnings and precautions: Angioedema can occur, and may be associated with life threatening respiratory compromise requiring emergency treatment. Hypersensitivity reactions can occur. Pregabalin should be discontinued immediately in these patients. Pregabalin should be used with caution in New York Heart Association (NYHA) Class III or IV cardiac failure patients. Pregabalin may cause dizziness and somnolence and impair patients' ability to drive or operate machinery. Pregabalin may increase the risk of suicidal thoughts or behavior. Dosage reduction in patients with renal dysfunction is necessary. Pregabalin should be tapered gradually over a minimum of 1 week. Abrupt discontinuation may lead to symptoms of physical dependence. Pregnancy and lactation: Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A decision to discontinue nursing or to discontinue the drug, should take into account the importance of the drug to the mother. Adverse reactions: Most common adverse reactions include dizziness, somnolence, dry mouth, ataxia, confusion, constipation, asthenia, incoordination, edema, blurred vision, weight gain and difficulty with concentration/attention.

Reference: Based on Pack Insert version Nov 2014.

For complete prescribing information please contact: Johnson & Johnson Ltd, 501 Arena Space,  
Off JVLR, Behind Majas Depot, Jogeshwari East, Mumbai - 400060

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# DRUG PROFILE

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

NRx

D-Trans Fentanyl Transdermal Patches

## Durogesic\*

### QUALITATIVE AND QUANTITATIVE COMPOSITION

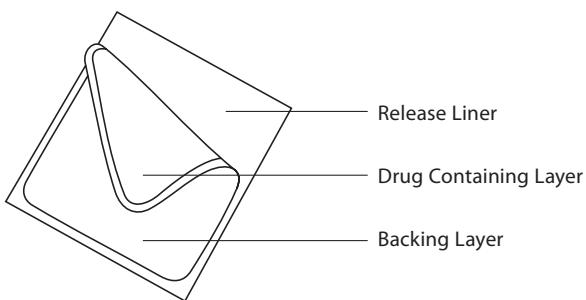
	Durogesic* Dosage (mcg/h)	Patch Size (cm <sup>2</sup> )	Fentanyl Content in Patch (mg)
Durogesic*	12 <sup>1</sup>	5.25	2.1
Durogesic*	25	10.5	4.2
Durogesic*	50	21.0	8.4
Durogesic*	75	31.5	12.6
Durogesic*	100	42.0	16.8

1 The lowest dose is designated as 12 mcg/h (however, the actual dose is 12.5 mcg/h) to distinguish it from a 125 mcg/h dose that could be prescribed by using multiple patches.

For excipients, see list of excipients.

### PHARMACEUTICAL FORM

Transdermal patch providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.



### Clinical Particulars

#### *Therapeutic indications*

Durogesic\* is indicated in the management of chronic pain and intractable pain requiring opioid analgesia.

## Posology and Method of Administration

Durogesic® doses should be individualized based upon the status of the patient and should be assessed at regular intervals after application. The patches are designed to deliver approximately 12, 25, 50, 75, and 100 mcg/h fentanyl to the systemic circulation, which represent about 0.3, 0.6, 1.2, 1.8, and 2.4 mg per day (see Qualitative and Quantitative Composition), respectively.

### Initial Dosage Selection

The appropriate initiating dose of Durogesic® should be based on the patient's current opioid use. It is recommended that Durogesic® be used in patients who have demonstrated opioid tolerance. Other factors to be considered are the current general condition and medical status of the patient, including body size, age, and extent of debilitation as well as degree of opioid tolerance.

### Adults

#### Opioid-tolerant Patients

To convert opioid-tolerant patients from oral or parenteral opioids to Durogesic® refer to Equianalgesic potency conversion below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/h to achieve the lowest appropriate dose of Durogesic® depending on response and supplementary analgesic requirements.

#### Opioid-naïve Patients

Clinical experience with Durogesic® is limited in opioid-naïve patients. In the circumstance in which therapy with Durogesic® is considered appropriate in opioid-naïve patients, it is recommended that these patients be titrated with low doses of immediate release opioids (e.g., morphine, hydromorphone, oxycodone, tramadol, and codeine) to attain equianalgesic dosage relative to Durogesic® with a release rate of 25 mcg/h. Patients can then be converted to Durogesic® 25 mcg/h. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/h to achieve the lowest appropriate dose of Durogesic® depending on response and supplementary analgesic requirements (see Equianalgesic potency conversion below). (see also Section Special warnings and special precautions for use: Opioid naïve and not opioid-tolerant states.)

### Equianalgesic Potency Conversion

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table 1. All IM and oral doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect.
3. To derive the Durogesic® dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use the dosage-conversion Table 2 [or the dosage-conversion Table 3] as follows:
  - a) Table 2 is for adult patients who have a need for rotation of, or conversion from, another opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).
  - b) Table 3 is for adult patients who are on a stable, and well-tolerated, opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).



**Table 1: Equianalgesic potency conversion**

Drug name	Equianalgesic dose (mg)	
	IM*	Oral
Morphine	10	30 (assuming repeated dosing)**
Hydromorphone	1.5	7.5
Methadone	10	20
Oxycodone	15	30
Levorphanol	2	4
Oxymorphone	1	10 (rectal)
Diamorphine	5	60
Pethidine	75	—
Codeine	130	200
Buprenorphine	0.4	0.8 (sublingual)

\* Based on single-dose studies in which an IM dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

\*\* The oral/IM potency for morphine is based on clinical experience in patients with chronic pain.

**Reference:** Foley KM. The treatment of cancer pain. *NEJM* 1985; 313 (2): 84-95.

**Table 2: Recommended starting dosage of Durogesic\* based upon daily oral morphine dose<sup>1</sup>**

Oral 24-hour morphine (mg/day)	Durogesic* dosage (mcg/h)
<135 (for adults)	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

1 In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to Durogesic\*



**Durogesic®**

fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**

Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**

(Tramadol 37.5 mg + Paracetamol 325 mg)

**Table 3: Recommended starting dosage of Durogesic\* based upon daily oral morphine dosage  
(for patients on stable and well tolerated opioid therapy)**

Oral 24-hour morphine (mg/day)	Durogesic* Dosage (mcg/h)
< 44	12
45-89	25
90-149	50
150-209	75
210-269	100
270-329	125
330-389	150
390-449	175
450-509	200
510-569	225
570-629	250
630-689	275
690-749	300

Initial evaluation of the maximum analgesic effect of Durogesic\* cannot be made before the patch is worn for 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.

Previous analgesic therapy should therefore be gradually phased out after the initial dose application until analgesic efficacy with Durogesic\* is attained.

#### **Dose Titration and Maintenance Therapy**

A 12 mcg/h strength is available for dose titration. The Durogesic\* patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained. If analgesia is insufficient after the initial application the dose may be increased after 3 days. Thereafter, dose adjustment can take place every 3 days. During initial phase of the therapy, some patients may not achieve adequate analgesia during the third day using this dosing interval and may require Durogesic\* patch to be applied at 48 hours rather than at 72 hours. Reducing the duration of system application by replacing the system before the 72 hours may result in increased serum concentrations of fentanyl (see Section Pharmacokinetic properties).

Dosage titration should normally be performed in 12 mcg/h or 25 mcg/h increments, although the supplementary analgesic requirements (oral morphine 45/90mg/day  $\approx$  Durogesic\* 12/25mcg/h) and pain status of the patient should be taken into account. More than one Durogesic\* patch may be used for doses greater than 100mcg/h. Patients may require periodic supplemental doses of a short-acting analgesic for "breakthrough" pain. Some patients may require additional or alternative methods of opioid administration when the Durogesic\* dose exceeds 300 mcg/h.



### *Discontinuation of Durogesic\**

If discontinuation of Durogesic\* is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because while fentanyl concentrations fall gradually after Durogesic\* is removed, it takes 17 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid analgesia should be gradual in order to prevent withdrawal symptoms.

Opioid withdrawal symptoms (See Undesirable Effects) are possible in some patients after conversion or dose adjustment. Table 2 and Table 3 should not be used to convert from Durogesic\* to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

### **Contraindications**

Durogesic\* is contraindicated in patients with known hypersensitivity to fentanyl or to the adhesives present in the patch.

Durogesic\* is contraindicated for the management of acute or postoperative pain because there is no opportunity for dose titration during short-term use and because serious or life-threatening hypoventilation could result.

### **Special warnings and special precautions for use**

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER DUROGESIC\* REMOVAL, OR MORE, AS CLINICAL SYMPTOMS DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER.

*Durogesic\* should be kept out of reach of children before and after use.*

*Do not cut Durogesic\* patches. A patch that has been divided, cut, or damaged in any way should not be used.*

#### **Opioid-naïve and Not Opioid -tolerant States:**

Use of Durogesic\* transdermal system in the opioid-naïve patient has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of Durogesic\* transdermal system is used in initiating therapy in opioid naïve patients. It is recommended that Durogesic\* be used in patients who have demonstrated opioid tolerance. (See Posology and method of administration: Initial dosage selection, Adults)

#### **Respiratory Depression**

As with all potent opioids, some patients may experience significant respiratory depression with Durogesic\* patients must be observed for these effects. Respiratory depression may persist beyond the removal of the Durogesic\* patch. The incidence of respiratory depression increases as the Durogesic\* dose is increased (see Section Overdose, concerning respiratory depression). CNS active drugs may increase the respiratory depression (see Interactions with other medicinal products and other forms of interaction).

#### **Chronic Pulmonary Disease**

Durogesic\* may have more severe adverse effects in patients with chronic obstructive, or other pulmonary disease. In such patients, opioids may decrease respiratory drive and increase airway resistance.

#### **Drug Dependence and Potential for Abuse**

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is rare.

Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of Durogesic® may result in overdose and/or death. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction.

#### ***Increased Intracranial Pressure***

Durogesic® should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO<sub>2</sub> retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Durogesic® should be used with caution in patients with brain tumors.

#### ***Cardiac Disease***

Fentanyl may produce bradycardia and should therefore be administered with caution to patients with bradyarrhythmias.

#### ***Hepatic Impairment***

Because fentanyl is metabolized to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive Durogesic®, they should be observed carefully for signs of fentanyl toxicity and the dose of Durogesic® reduced if necessary (see Section Pharmacokinetic properties).

#### ***Renal Impairment***

Less than 10% of fentanyl is excreted unchanged by the kidney and, unlike morphine, there are no known active metabolites eliminated by the kidney. If patients with renal impairment receive Durogesic®, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section Pharmacokinetic properties).

#### ***Fever/External Heat Application***

A pharmacokinetic model suggests that serum fentanyl concentrations may increase by about one-third if the skin temperature increases to 40°C. Therefore, patients with fever should be monitored for opioid side effects and the Durogesic® dose should be adjusted if necessary.

**There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the Durogesic® system increased mean fentanyl AUC values by 120% and mean C<sub>max</sub> values by 61%.**

All patients should be advised to avoid exposing the Durogesic® application site to direct external heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, intensive sunbathing, hot water bottles, prolonged hot baths, saunas and hot whirlpool spa baths.

#### ***Serotonin Syndrome***

Caution is advised when Durogesic® is coadministered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

If serotonin syndrome is suspected, treatment with Durogesic® should be discontinued.

**Durogesic®**  
fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**  
Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**  
(Tramadol 37.5 mg + Paracetamol 325 mg)



### **Interactions with other medicinal products**

#### **Interactions with CYP3A4 Inhibitors**

The concomitant use of Durogesic\* with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, neflifinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation special patient care and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patient is closely monitored. Patients, especially those who are receiving Durogesic\* and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

#### **Accidental Exposure by Patch Transfer**

Accidental transfer of a fentanyl patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer (See Section Overdose).

#### **Use in Elderly Patients**

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. If elderly patients receive Durogesic\*, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section Pharmacokinetic properties).

#### **Gastrointestinal Tract**

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with Durogesic\* should be stopped.

### **Interaction with other medicinal products and other forms of interaction**

The concomitant use of other central nervous system depressants, including opioids, sedatives, hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages, may produce additive depressant effects; hypoventilation, hypotension, and profound sedation, coma or death may occur. Therefore, the use of any of these drugs concomitantly with Durogesic\* requires special patient care and observation.

Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4.

The concomitant use of CYP3A4 inhibitors with transdermal fentanyl may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (see also Section Special warnings and special precautions for use).

The concomitant use with CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin) could result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. This may require a dose adjustment of transdermal fentanyl. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and may result in a fentanyl plasma increase concentration which could increase or prolong both the therapeutic

and adverse effects, and may cause serious respiratory depression. In this situation, careful monitoring and dose adjustment should be made if warranted.

#### **Monoamine Oxidase Inhibitors (MAOI)**

Durogesic\* is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported. Therefore, Durogesic\* should not be used within 14 days after discontinuation of treatment with MAOIs.

#### **Serotonergic Drugs**

Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

#### **Pregnancy and lactation**

There are no adequate data from the use of Durogesic\* in pregnant women. Studies in animals have shown some reproductive toxicity (see Section Preclinical safety data). The potential risk for humans is unknown, although fentanyl as an IV anesthetic has been found to cross the placenta in early human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Durogesic\* during pregnancy. Durogesic\* should not be used during pregnancy unless clearly necessary.

Use of Durogesic\* during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see Section Contraindications). Moreover, because fentanyl passes through the placenta, the use of Durogesic\* during childbirth might result in respiratory depression in the newborn infant.

Fentanyl is excreted into human milk and may cause sedation/respiratory depression in an infant. Therefore, Durogesic\* is not recommended for use in nursing women.

#### **Effects on ability to drive and use machines**

Durogesic\* may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

#### **Undesirable effects**

##### **Clinical Trial Data**

The safety of Durogesic\* was evaluated in 216 subjects who participated in a multicenter, double-blind, randomized, placebo-controlled clinical trial (FEN-EMA-1) of Durogesic\*. These subjects took at least one dose of Durogesic\* and provided safety data. This trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement. Patients were treated for 6 weeks with Durogesic\* by titrating to adequate pain control starting from 25 mcg/h to a maximum dose of 100 mcg/h in 25 mcg/h increments. Adverse drug reactions (ADRs) reported for ≥1% of Durogesic\*-treated subjects and with an incidence greater than placebo-treated subjects were anorexia, insomnia, depression, somnolence, dizziness, vertigo, palpitations, nausea, vomiting, constipation, abdominal pain, dry mouth, pruritus, rash, muscle spasm, fatigue, malaise, asthenia and peripheral edema.

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesic to Durogesic\* or if therapy is stopped suddenly (see Section Posology and method of administration). There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used Durogesic\* during pregnancy (see Section, Pregnancy and lactation).

**Durogesic®**  
fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**  
Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**  
(Tramadol 37.5 mg + Paracetamol 325 mg)



### Overdose

#### Symptoms

The manifestations of fentanyl overdosage are an extension of its pharmacologic actions, the most serious effect being respiratory depression.

#### Treatment

For management of respiratory depression, immediate countermeasures include removing the Durogesic\* patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube, and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, hypovolemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

### PHARMACOLOGICAL PROPERTIES

#### Pharmacodynamic properties

Pharmacotherapeutic group: opioids; phenylpiperidine derivatives, ATC code: N02AB03

Fentanyl is an opioid analgesic, interacting predominantly with the  $\mu$ -opioid receptor. Its primary therapeutic actions are analgesia and sedation. Minimum effective analgesic serum concentrations of fentanyl in opioid-naïve patients range from 0.3 to 1.5 ng/mL; side effects increase in frequency at serum concentrations above 2 ng/mL. Both the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

#### Pharmacokinetic properties

##### Absorption

Durogesic\* provides continuous systemic delivery of fentanyl during the 72-hour application period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the system and the lower concentration in the skin drives drug release. After initial Durogesic\* application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72-hour application period. The serum fentanyl concentrations attained are proportional to the Durogesic\* patch size. By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size.

A pharmacokinetic model has suggested that serum fentanyl concentrations may increase by 14% (range 0- 26%) if a new patch is applied after 24 hours rather than the recommended 72-hour application.

##### Distribution

The plasma-protein binding of fentanyl is about 84%.

##### Metabolism

Fentanyl is a high clearance drug and is rapidly and extensively metabolized primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell

assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

#### **Elimination**

After Durogesic\* is removed, serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13-22) hours following a 24-hour application. Following a 72-hour application, the mean half-life ranges from 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3-12) hours.

Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the feces, primarily as metabolites.

#### **Special Populations**

##### *Elderly*

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. In a study conducted with Durogesic\*, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section Special warnings and special precautions).

##### *Hepatic Impairment*

A study conducted in patients with hepatic cirrhosis, the pharmacokinetics of a single 50 µg/hr application of Durogesic\* were assessed. Although  $t_{max}$  and  $t_{1/2}$  were not altered, the mean plasma  $C_{max}$  and AUC values increased by approximately 35% and 73%, respectively, in these patients. Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of Durogesic\* reduced if necessary (see Section Special warnings and special precautions).

##### *Renal Impairment*

Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive Durogesic\*, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section Special warnings and special precautions).

#### **Preclinical safety data**

*In vitro* fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in vivo rodent studies and bacterial assays. In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females (0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/h patch based on AUC<sub>0-24h</sub> comparison).

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

## **PHARMACEUTICAL PARTICULARS**

### **List of excipients**

Backing layer: Polyester\*/EVA\*\*

Drug layer: Polyacrylate adhesive

Protective liner: Siliconized polyester

**Durogesic®**  
fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**  
Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**  
(Tramadol 37.5 mg + Paracetamol 325 mg)



Inks (on backing): Orange/Red/Green/Blue/Gray printing ink

\* Polyester = Polyethylene terephthalate

\*\* EVA = Ethyl vinyl acetate

### Incompatibilities

None known.

### Shelf life

See outer carton for expiry date

### Special precautions for storage

Store in original unopened pouch.

- Keep out of reach of children.
- Nature and contents of container

Each Durogesic\* patch is packed in a heat-sealed pouch and is supplied in cartons containing 5 pouches.

### Instructions for use/handling

Durogesic\* should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of Durogesic\* application requires cleansing prior to application of the patch, this should be done with clear water. Soaps, oils, lotions, or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to the use. Patches that are cut, divided, or damaged in any way should not be used.

Durogesic\* should be applied immediately upon removal from the sealed package. To remove the patch from the protective pouch, locate the pre-cut notch (indicated by an arrow on the patch label) along the edge of the seal. Fold the pouch at the notch, then carefully tear the pouch material. Further open the pouch along both sides, folding the pouch open like a book. The release liner for the patch is slit. Fold the patch in the middle and remove each half of the liner separately. Avoid touching the adhesive side of the patch. Apply the patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make sure that the edges of the patch are adhering properly. Then wash hands with clean water.

Durogesic\* may be worn continuously for 72 hours. A new patch should be applied to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of the skin.

Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded. Unused patches should be returned to the (hospital) pharmacy.

Wash hands, with water only, after applying or removing the patch.

**"Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only".**

### Manufactured by:

Janssen Pharmaceutica NV, Beerse, Belgium

### Imported by:

Johnson and Johnson Private Limited,  
Gala No. 1 to 10, BLDG. No. J-2, Ground Floor, Shree Arihant Complex,  
Kalher, Thane-Bhiwandi Road, Thane – 421302.

### Marketed in India by:

Johnson and Johnson Private Limited,  
L.B.S. Marg, Mulund (West), Mumbai 400080

Reference: Company Core Data Sheet (CCDS) dated 24 July 2013.

# DRUG PROFILE

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

Pregabalin & Mecobalamin Capsules

## PRELOGIC

### Composition

Each hard gelatin capsule contains: Pregabalin IP 75 mg, Mecobalamin JP 750 mcg

Appropriate overages of vitamin added; approved colours used in the capsule shell.

### Description

Pregabalin is a structural analogue of the naturally occurring gamma amino butyric acid (GABA). Pregabalin is described chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is  $C_6H_{17}NO_2$  and the molecular weight is 159.23. It is freely soluble in water and both basic and acidic aqueous solutions.

Mecobalamin is a form of vitamin  $B_{12}$ . Chemically it is  $Co\alpha-[{\alpha}-(5,6-Dimethylbenz-1H-imidazolyl)]-Co\beta\text{-methylcobamide}$  with molecular formula of  $C_{63}H_{91}CoN_{13}O_{14}P$  and molecular weight of 1344 g/mol. It is sparingly soluble in water, slightly soluble in ethanol, and practically insoluble in acetonitrile. It is affected by light. Mecobalamin is used in peripheral neuropathy and diabetic neuropathy.

### Clinical Pharmacology

#### Pharmacodynamics

Pregabalin binds with high affinity to the  $\alpha\delta$  site (an auxilliary subunit of voltage-gated calcium channels) in central nervous system tissues. Exact mechanism of action of pregabalin is unknown. While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to  $GABA_A$ ,  $GABA_B$ , or benzodiazepine receptors.

Mecobalamin is one of two active coenzymes used by  $B_{12}$  dependent enzymes in the body, and is specifically the  $B_{12}$  form used by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), also known as methionine synthase involved in methionine synthesis. Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis. Mecobalamin promotes axonal transport and axonal regeneration. Mecobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipids, and increases myelination of neurons.

#### Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours. Peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is  $\geq 90\%$  and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. Administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin undergoes negligible metabolism in humans. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Pregabalin elimination is nearly

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Fentanyl transdermal system  
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(Tramadol 37.5 mg + Paracetamol 325 mg)

proportional to creatinine clearance (CLcr).

Mecobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B<sub>12</sub>. The quantity of cobalamin detected following a small oral dose of Mecobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of Mecobalamin. Human urinary excretion of Mecobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention.

### Indications

For the treatment of adult patients with peripheral neuropathy.

### Dosage and Administration

As directed by the Physician.

### Contraindications

Hypersensitivity to any component(s) of this formulation.

### Warnings

Angioedema (e.g. swelling of the throat, head and neck) can occur, and maybe associated with life threatening respiratory compromise requiring emergency treatment. Pregabalin should be discontinued immediately in these cases.

Hypersensitivity reactions (e.g. hives, dyspnea, and wheezing) can occur. Pregabalin should be discontinued immediately in these patients.

Pregabalin may cause peripheral edema. Exercise caution when co-administering pregabalin and thiazolidinedione antidiabetic agents. Hence, pregabalin should be used with caution in New York Heart Association (NYHA) Class III or IV cardiac failure patients.

Pregabalin may cause dizziness and somnolence and impair patients' ability to drive or operate machinery.

Antiepileptic drugs (AEDs), including Pregabalin may increase the risk of suicidal thoughts or behavior in patients taking these drugs.

Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Patients should be informed that if changes in vision occur, they should notify their physician.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if marked elevated creatine kinase levels occurs.

### Precautions:

#### *Use in Special Populations*

**Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known if pregabalin is excreted in human milk; because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and efficacy of pregabalin in paediatric patients have not been established.

**Geriatric Use:** Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

**Renal insufficiency:** Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. For patients on hemodialysis, dosing must be modified.

### Drug Interactions

No clinically significant drug interactions.

### Adverse Reactions

Most common adverse reactions with pregabalin are dizziness, somnolence, dry mouth, ataxia, confusion, asthenia, incoordination, edema, blurred vision, weight gain and difficulty with concentration/attention.

### Drug Abuse and Dependence

Physician should carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, and drug-seeking behaviour). Abrupt discontinuation may lead to symptoms of physical dependence.

### Overdosage

There is limited experience with overdose of pregabalin. Elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

### Storage

Store in a cool, dry and dark place.

Keep out of reach of children.

### Presentation

A blister of 10 capsules.

### Manufactured by

#### Emcure Pharmaceuticals Ltd.

SIDCO Industrial Complex, Lane No. 3, Phase-II,  
Bari-Brahmana, Jammu (J & K) – 181 133.

#### Marketed in India by:

Johnson and Johnson Private Limited,  
L.B.S. Marg, Mulund (West), Mumbai 400080

# DRUG PROFILE

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

Acetaminophen & Tramadol Hydrochloride Tablets USP

## ULTRACET®/ULTRACET® Semi

**QUALITATIVE AND QUANTITATIVE COMPOSITION:** ULTRACET®/ULTRACET® Semi is available as tablets for oral administration containing 37.5/18.75 mg tramadol hydrochloride and 325/162.5 mg acetaminophen.

**PHARMACEUTICAL FORM:** ULTRACET®/ULTRACET® Semi is available as a light yellow, film-coated, biconvex, capsule-shaped tablet.

### CLINICAL PARTICULARS

**Therapeutic Indications:** ULTRACET®/ULTRACET® Semi is indicated for the management of severe acute pain.

**Posology and Method of Administration:** Unless otherwise prescribed, ULTRACET®/ULTRACET® Semi should be administered as follows:

**Adults and children over 16 years:** ULTRACET®/ULTRACET® Semi should not be used for more than 5 days when used for the treatment of severe acute pain.

The maximum single dose of ULTRACET®/ULTRACET® Semi is 1 to 2 tablets every 4 to 6 hours as needed for pain relief, up to per day maximum equivalent to 300 mg tramadol hydrochloride and 2.6 g acetaminophen.

ULTRACET®/ULTRACET® Semi can be administered without regard to food.

**Pediatric (children below 16 years):** The safety and effectiveness of ULTRACET®/ULTRACET® Semi has not been established in the pediatric population.

**Elderly (geriatric):** No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥65 years of age and younger subjects.

**CONTRAINdications:** ULTRACET®/ULTRACET® Semi should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids. It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.

### SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

**Seizures:** Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking: Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or Opioids.

Administration of tramadol may enhance the seizure risk in patients taking: MAO inhibitors, Neuroleptics or other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

**Anaphylactoid reactions:** Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET®/ULTRACET® Semi.

**Respiratory depression:** Administer ULTRACET®/ULTRACET® Semi cautiously in patients at risk for respiratory depression. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

#### CYP2D6 ULTRA-RAPID METABOLISM OF TRAMADOL

Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may result in higher than expected serum M1 levels which could lead to an increased risk of respiratory depression (see section Human Experience - Tramadol). Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolizers (see section Pharmacokinetic Properties - Metabolism).

**Use with CNS depressants:** ULTRACET®/ULTRACET® Semi should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics.

**Increased intracranial pressure or head trauma:** ULTRACET®/ULTRACET® Semi should be used with caution in patients with increased intracranial pressure or head injury.

**Use in opioid-dependent patients:** ULTRACET®/ULTRACET® Semi should not be used in opioid-dependent patients. Tramadol has shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids.

**Use with alcohol:** Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use.

**Withdrawal:** Withdrawal symptoms may occur if ULTRACET®/ULTRACET® Semi is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus, and unusual CNS symptoms have also been very rarely reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

**Use with MAO inhibitors and serotonin reuptake inhibitors:** Use ULTRACET®/ULTRACET® Semi with great caution in patients taking monoamine oxidase inhibitors. Concomitant use of tramadol with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

**Use in renal disease:** ULTRACET®/ULTRACET® Semi has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET®/ULTRACET® Semi should not exceed 2 tablets/12 hours.

**Use in hepatic disease:** The use of ULTRACET®/ULTRACET® Semi in patients with severe hepatic impairment is not recommended.

**Serious skin reactions:** Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving acetaminophen. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

#### HYponatremia

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**ULTRACET®**  
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Hyponatremia has been reported very rarely with the use of ULTRACET®/ULTRACET® Semi, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia. In some reports, this hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of ULTRACET®/ULTRACET® Semi and appropriate treatment (e.g. fluid restriction). During ULTRACET®/ULTRACET® Semi treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

**Precautions general:** The recommended dose of ULTRACET®/ULTRACET® Semi should not be exceeded.

ULTRACET®/ULTRACET® Semi should not be co-administered with other tramadol or acetaminophen containing products.

### ***Interactions with Other Medicinal Products and Other Forms of Interaction***

**Use with MAO inhibitors and serotonin reuptake inhibitors:** Interaction with MAO inhibitors have been reported for some centrally acting drugs. (See section Withdrawal).

**Use with carbamazepine:** Concomitant administration of tramadol hydrochloride and carbamazepine causes a significant increase in tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect from the tramadol component of ULTRACET®/ULTRACET® Semi.

**Use with quinidine:** Tramadol is metabolized to M1 by CYP2D6. Concomitant administration of quinidine and tramadol results in increased concentrations of tramadol. The clinical consequences of these findings are unknown.

**Use with warfarin-like compounds:** As medically appropriate, periodic evaluation of prothrombin time should be performed when ULTRACET®/ULTRACET® Semi and these agents are administered concurrently due to reports of increased INR in some patients.

**Use with inhibitors of CYP2D6:** *In-vitro* drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

**Use with cimetidine:** Concomitant administration of ULTRACET®/ULTRACET® Semi and cimetidine has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

**Pregnancy and lactation:** Tramadol has been shown to cross the placenta.

There are no adequate and well-controlled studies in pregnant women.

Safe use in pregnancy has not been established. ULTRACET®/ULTRACET® Semi is not recommended for nursing mothers because its safety in infants and newborns has not been studied.

**Effects on ability to drive and use machines:** ULTRACET®/ULTRACET® Semi may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

**Undesirable Effects:** The most frequently reported events were in the central nervous system and gastrointestinal system.

The most common reported events were nausea, dizziness, and somnolence.

In addition, the following effects have been frequently observed, though the frequency is generally low:

*Body as a Whole* – Asthenia, fatigue, hot flushes

*Central and Peripheral Nervous System* – Headache, tremor

*Gastrointestinal System* – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, vomiting

*Psychiatric Disorders* – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness

*Skin and Appendages* – Pruritus, rash, increased sweating

Uncommon reported clinically significant adverse experiences with at least a possible causal link to ULTRACET®/ULTRACET® Semi include:

*Body as a Whole* – Chest pain, rigors, syncope, withdrawal syndrome

*Cardiovascular Disorders* – Hypertension, aggravated hypertension, hypotension

*Central and Peripheral Nervous System* – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo

*Gastrointestinal System* – Dysphagia, melena, tongue edema

*Hearing and Vestibular Disorders* – Tinnitus

*Heart Rate and Rhythm Disorders* – Arrhythmia, palpitation, tachycardia

*Liver and Biliary System* – Liver test abnormalities

*Metabolic and Nutritional Disorders* – Weight decrease

*Psychiatric Disorders* – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking *Red Blood Cell Disorders* – Anemia

*Red Blood Cell Disorders* – Anemia

*Respiratory System* – Dyspnea

*Urinary System* – Albuminuria, micturition disorder, oliguria, urinary retention

*Vision Disorders* – Abnormal vision

**Other clinically significant adverse experiences previously reported in clinical trials or postmarketing reports with tramadol hydrochloride:** Other events which have been reported with the use of tramadol products include: orthostatic hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson Syndrome/TENS), cognitive dysfunction, suicidal tendency, and hepatitis. Reported laboratory abnormalities included elevated creatinine. Serotonin syndrome (whose symptoms may include fever, excitation, shivering and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAO inhibitors. Post-marketing experience with the use of tramadol containing products included rare reports of delirium, miosis, mydriasis, and speech disorder, and very rare reports of movement disorder. Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times. Cases of hypoglycemia have been reported very rarely in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients. Cases of hyponatremia and/or SIADH have been reported very rarely in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medications that may cause hyponatremia.

**Other clinically significant adverse experiences previously reported in clinical trials or postmarketing reports with acetaminophen:** Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by



discontinuation of the drug, and when necessary, symptomatic treatment. There have been several reports that suggest that acetaminophen may produce hypoprothrombinemia when administered with warfarin like compounds. In other studies, prothrombin time did not change.

**Overdose:** ULTRACET®/ULTRACET® Semi is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. The initial symptoms of tramadol over dosage may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

**Human experience: Tramadol:** Serious potential consequences of overdosage of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death.

**Acetaminophen:** Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic overdosage may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

**Treatment:** A single or multiple overdose with ULTRACET®/ULTRACET® Semi may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

In treating an overdosage of ULTRACET®/ULTRACET® Semi, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Measures should be taken to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

In adult and pediatric patients, any individual presenting with an unknown amount of acetaminophen ingested or with a questionable or unreliable history about the time of ingestion should have a plasma acetaminophen level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated acetaminophen ingestion exceeds 7.5 to 10 grams for adults and adolescents or 150 mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

### PHARMACOLOGICAL PROPERTIES

**Chemical Names:** TRAMADOL HYDROCHLORIDE

(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

ACETAMINOPHEN: N-acetyl-p-aminophenol (4-hydroxyacetanilide).

**PHARMACODYNAMIC PROPERTIES:** Tramadol is a centrally acting analgesic compound. At least two complementary mechanisms appear applicable, binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Acetaminophen is another centrally acting analgesic. The exact site and mechanism of its analgesic action is not clearly defined.

When evaluated in a standard animal model, the combination of tramadol and acetaminophen exhibited a synergistic effect.

### PHARMACOKINETIC PROPERTIES

**General:** Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one ULTRACET®/ULTRACET® Semi tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

After a single oral dose of one Tramadol/Acetaminophen combination tablet (37.5 mg/325 mg) peak plasma concentrations of 64.3/55.5 ng/ml [(+)-Tramadol/(-)-Tramadol] and 4.2 µg/ml (acetaminophen) are reached after 1.8 h [(+)-Tramadol/(-)-Tramadol] and 0.9 h (acetaminophen), respectively. Mean elimination half lives  $t_{1/2}$  are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (acetaminophen).

Single and multiple dose pharmacokinetic studies of ULTRACET®/ULTRACET® Semi in volunteers showed no significant drug interactions between tramadol and acetaminophen.

**Table 1: Summary of Mean ( $\pm$ SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers**

Parameter <sup>a</sup>	(+) -Tramadol		(-) -Tramadol		(+)-M1		(-)-M1		Acetaminophen	
C <sub>max</sub> (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t <sub>max</sub> (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
CL/F (mL/min)	588	(226)	736	(244)	—	—	—	—	365	(84)
t <sub>1/2</sub> (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

<sup>a</sup>For acetaminophen, C<sub>max</sub> was measured as µg/mL.

**Absorption:** Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two ULTRACET®/ULTRACET® Semi tablets occurs at approximately two and three hours, respectively, post-dose in healthy adults.

Oral absorption of acetaminophen following administration of ULTRACET®/ULTRACET® Semi is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of acetaminophen occur within 1 hour and are not affected by co-administration with tramadol.

**Food effects:** The oral administration of ULTRACET®/ULTRACET® Semi with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or acetaminophen, so that ULTRACET®/ULTRACET® Semi can be taken independently of meal times.

**Distribution:** The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20%.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg.

A relative small portion (~20%) of acetaminophen is bound to plasma protein.

**Durogesic®**  
fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**  
Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**  
(Tramadol 37.5 mg + Paracetamol 325 mg)



**Metabolism:** Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of ULTRACET®/ULTRACET® Semi in volunteers showed no significant change compared to dosing with tramadol alone.

Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. Tramadol is extensively metabolized by a number of pathways, including CYP2D6. Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients (see section CYP2D6 Ultra-rapid Metabolism of Tramadol). The prevalence of this CYP2D6 genotype varies by population and has been reported in literature to range from 1% to 10% in African Americans, Caucasian Americans, Asians and Europeans (including specific studies in Greeks, Hungarians and Northern Europeans) to as high as 29% in African/Ethiopians.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principle separate pathways:

- Conjugation with glucuronide
- Conjugation with sulfate
- Oxidation via cytochrome P450 enzyme pathway.

**Elimination:** Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of racemic tramadol and M1 are approximately six and seven hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing of ULTRACET®/ ULTRACET® Semi.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

### Preclinical Safety Data

**Tramadol/acetaminophen combination:** There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

No drug-related teratogenic effects were observed in the progeny of rats treated orally with the combination of tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose (50/434 mg/kg tramadol/acetaminophen) 8.3 times the maximum human dose but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. Lower and less severe maternally toxic dosages (10/87 and 25/217 mg/kg tramadol/acetaminophen) did not produce embryo or fetal toxicity.

**Tramadol hydrochloride:** *Carcinogenicity/Mutagenicity:* A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice (dosing orally up to 30 mg/kg for approximately two years, although the study was not done with the Maximum Tolerated Dose). This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study.

Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters.

Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

**Impairment of Fertility/Effect on Reproduction:** No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats.

Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (6 to 10 times the maximum human dose). No toxicity was observed for progeny of dams receiving 8, 10, 20, 25 or 40 mg/kg. Maternal toxicity was observed at all dose levels of tramadol in this study, but effects on progeny were evident only at higher dose levels where maternal toxicity was more severe.

#### PHARMACEUTICAL PARTICULARS

**List of excipients:** Powdered Cellulose USNF, Pregelatinised Starch IP, Sodium Starch Glycolate IP, Starch IP, Magnesium Stearate IP, Hydroxypropylmethylcellulose IP, Polyethylene glycol 400 BP, Polysorbate 80 IP, \*\* Purified Water IP (\*\* Does not appear in final product), Colorant – Yellow Oxide of Iron and Titanium Dioxide

**Incompatibilities:** None known

**Shelf Life:** See Mfg. date/Exp. Date printed on pack

**Special Precautions for Storage:** Preserve in tight containers. Store at controlled room temperature. Keep out of reach of children.

#### SCHEDULE H1 WARNING

It is dangerous to take this preparation except in accordance with the medical advice.  
Not to be sold by retail without the prescription of a Registered Medical Practitioner.

#### WARNINGS

Taking more than the recommended daily dose, may cause serious liver damage or allergic reactions (e.g. swelling of the face, mouth and throat, difficulty in breathing, itching or rash). In case of overdose, get medical help right away. Quick medical attention is critical even if you do not notice any signs or symptoms.

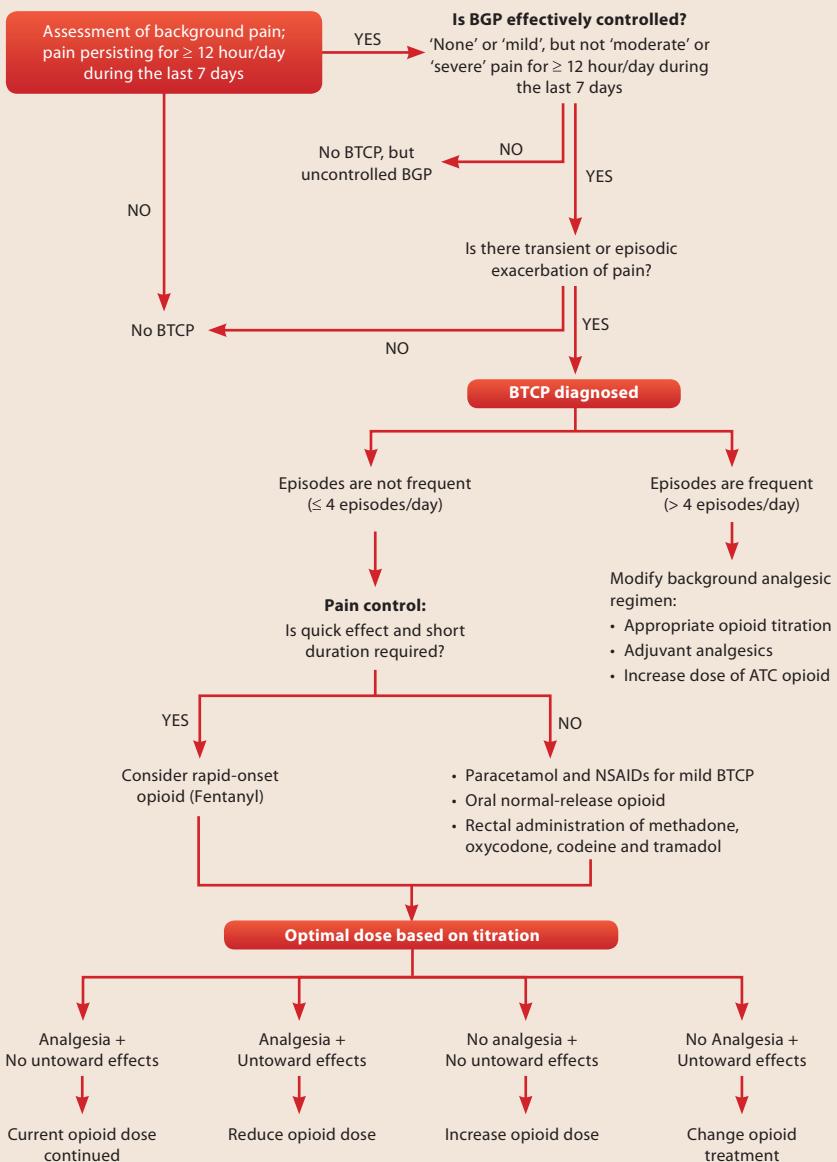
#### Made in India by

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\*Registered trademark of Johnson & Johnson, USA

**Reference:** Based on Company Core Data Sheet dated 23 Sep 2015.

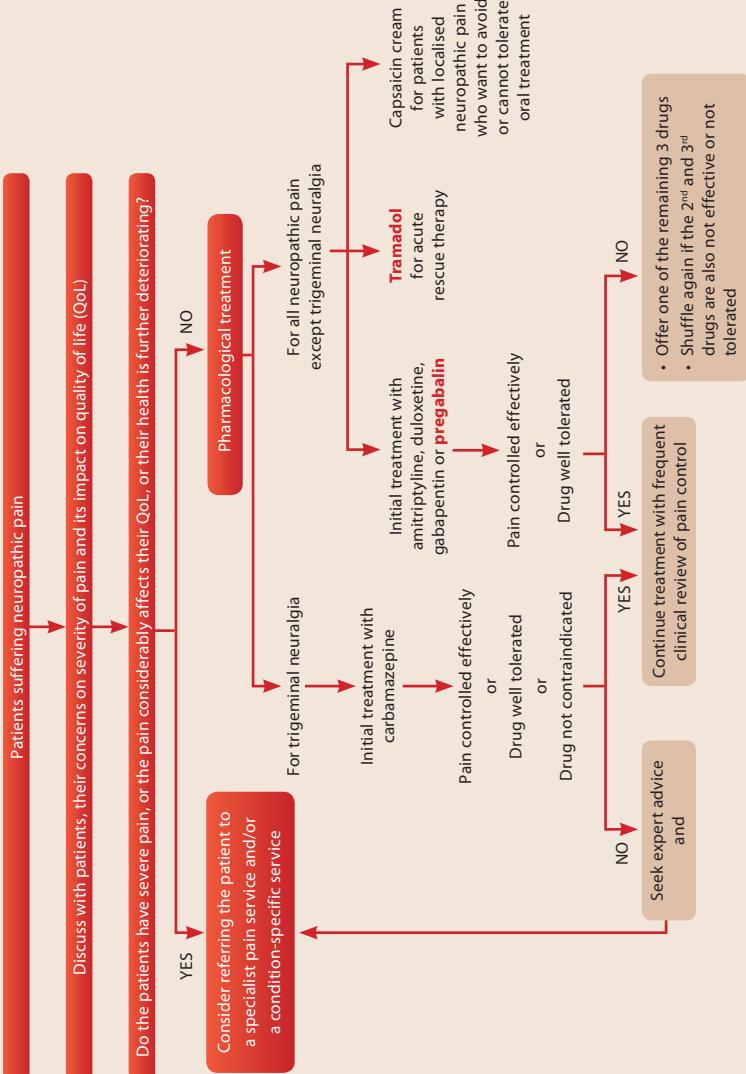
### Algorithm for diagnosis and management of breakthrough cancer pain



**Abbreviations:** BTCP: Breakthrough cancer pain; BGP: Background pain; ATC: Around-the-clock.

**Source:** Breakthrough cancer pain guidelines 2013. Available at: <http://www.cancernurse.eu/documents/EONSBreakthroughCancerPainGuidelines.pdf>. Accessed on 12.10.2016.

## Pharmacological management of neuropathic pain in non-specialist settings



Source: Neuropathic pain in adults: pharmacological management in non-specialist settings. Available at: <https://www.nice.org.uk/guidance/CG173>. Accessed on 12.10.2016.

## Blocking specific enzymes: A novel approach to stop aggressive brain tumor from spreading

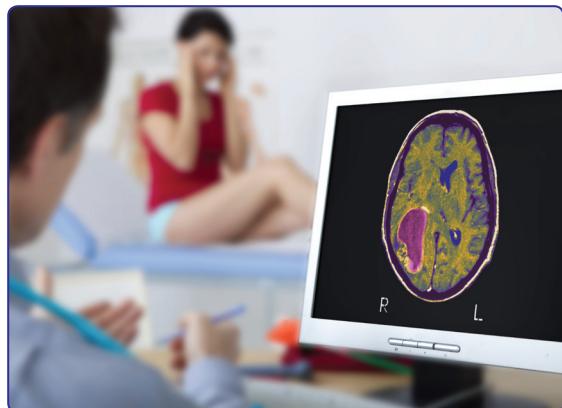
According to a study published in a leading journal, Molecular Neurobiology, researchers at the University of Southampton have identified a potential method of preventing the spread of glioblastoma, one of the most common forms of malignant brain tumors. These brain tumors are highly proliferative and infiltrative; the threadlike projections of these tumors reach out to other parts of the brain, rendering it difficult to remove them. Despite being made major advances in the management of leukemias and other cancers, the formation of glioblastomas and their infiltration to brain tissues remains poorly understood. The spread of these tumors, once prevented, could pave the way for enhanced patient survival.

The researchers isolated multipotent sphere-forming cells from human high grade glioma [glioma sphere-forming cells (GSCs)] and examined the adhesive and migratory properties of these cells in vitro. They further analyzed how certain enzymes such as metalloproteinases ADAM10 and ADAM17 affect the movement and function of the human tumor cells. It was observed that ADAM10 and ADAM17 inhibition selectively increased GSC, but not neural stem cell, migration and that the migrated GSCs displayed a differentiated phenotype.

The researchers deduced that the blockade of certain enzymes such as ADAM10 and ADAM17 may put a stop to the tumor growth and spread. In addition, it might also facilitate cancer cell migration away from the place of their growth. This in turn could make it easier to remove them through conventional cancer treatments such as radiotherapy, chemotherapy or surgery, ultimately improving survival rates.

### Sources:

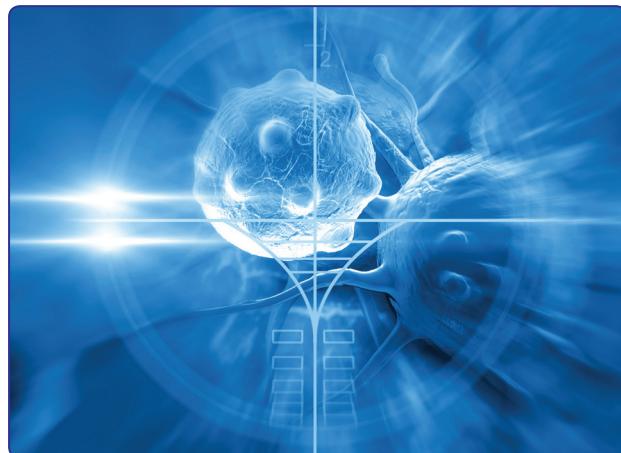
- New hope in fight against aggressive, often hard to treat brain tumor. Available at: <https://www.sciencedaily.com/releases/2016/09/160923083559.htm>. Accessed on 10.10.2016.
- Siney EJ, Holden A, Casselden E, Bulstrode H, Thomas GJ, Willaime-Morawek S Metalloproteinases ADAM10 and ADAM17 Mediate Migration and Differentiation in Glioblastoma Sphere-Forming Cells. Mol Neurobiol. 2016 Aug 19.



## Cancer patients and optimal pain relief: Opioid crisis of a different kind

According to a recent study at the University of Leeds, many terminal cancer patients are not getting adequate pain treatment early enough. The researchers reported that, on average, terminal cancer patients received their first prescription of a strong opioid, such as morphine, just nine weeks before their death. The problem, according to the researchers, is that the onset of pain usually occurs much earlier in these patients.

Using the UK Cancer Registry data, the researchers studied a sample of more than 6,000 patients who died of cancer between 2005 and 2012. They found that less than half (48%) of all study patients were prescribed a strong opioid, and in that cohort, an average of only four prescriptions was issued during the median duration of 9 weeks prior to death. Concern over ongoing



'opioid epidemic' in the developed countries may be inadvertently affecting the efforts to ameliorate pain in cancer patients. Data reported by the UK National Health and Social Care Information Center revealed that overall opioid prescribing increased by 466% between 2000 and 2010; however, for cancer patients, opioid prescribing increased by only about 16%.

Further, the researchers found median survival from diagnosis to be 60 weeks, indicating that most opioid prescribing in fact occurred late in the course between diagnosis and death, regardless of cancer duration. In addition, over 90% of all patients in the cohort had received some form of cancer treatment, thus refuting the notion that absence of or late cancer diagnosis hindered timely access to an opioid. Nonetheless, for cancer patients, there are apparently hindrances to accessing these drugs, which need to be acknowledged and overcome. The clinicians need to be aware of the potential for pain, conduct a meticulous pain assessment and physical examination, while deliberating pharmacologic and non-pharmacologic approaches that may be safe and effective.

**Source:** A Different Kind of Opioid Crisis in Cancer Patients. Available at: <http://www.medscape.com/viewarticle/869095>. Accessed on 10.10.2016.

## Novel molecular imaging approaches: A step closer to precision oncology

Innovative molecular imaging agents, together with improvements in more conventional imaging methods, may enhance the development of new targeted therapies, bringing precision oncology to the front, according to a recent overview of the latest imaging biomarkers. The researchers explain that precision oncology intends to amend the treatment decisions according to an individual tumor's molecular and genetic aspects, thus enhancing the prospect of a successful outcome. Various imaging-based predictive biomarkers are being studied lately and many of them are well established in the management of various tumors.

The glucose analog 2-deoxy-2 [<sup>18</sup>F] fluoro-D-glucose (<sup>18</sup>F-FDG) is one such clinical imaging probe. <sup>18</sup>F-FDG can detect early declines in metabolic activity, which in turn can help clinicians anticipate, before initiating a treatment, whether a patient will respond to chemotherapy. Another biomarker, [<sup>18</sup>F] fluoroestradiol (<sup>18</sup>F-FES), is already in use clinically. The <sup>18</sup>F-FES positron emission tomography (PET)-computed tomography (CT) can evaluate the binding potential of fulvestrant, an estrogen receptor (ER) antagonist, to ERs in patients with estrogen-positive breast cancer. It can also assess the dose of fulvestrant needed to destroy estrogen receptors. Furthermore, <sup>18</sup>F-fluorodihydrotestosterone (FDHT), yet another imaging pharmacodynamic biomarker, has been used to appraise optimal drug concentrations of apalutamide for the treatment of castration-resistant prostate cancer.

Importantly, three new molecular imaging agents, C-choline and <sup>18</sup>F fluciclovine for prostate cancer, and the somatostatin receptor ligand <sup>68</sup>Ga-DOTATATE for PET imaging, have been approved by the FDA since 2012. The combination of imaging and other biomarker data helps ascertain whether a particular therapy will result in a response in a patient and whether the patient is receiving the optimal dose.

**Source:** Molecular Imaging Brings Precision Oncology Closer to Clinic. Available at: <http://www.medscape.com/viewarticle/869139>. Accessed on 12.10.2016.

## Sticky nanoparticles: An alternative to conventional chemotherapy in the fight against cancer

Scientists have found that the use of sticky bioadhesive nanoparticles to deliver a potent chemotherapy drug may be a safer and more effective method of treating gynecological cancers than traditional treatments.

A drug called epothilone B (EB) has frequently been used in clinical trials to target tumor cells resistant to traditional chemotherapy agents. Although EB proved effective in these trials, its high toxicity caused severe side effects, precluding its further use. Therefore, to utilize EB effectively and simultaneously limit its deleterious adverse effects, the researchers encased it in a nanoparticle before injecting it into the peritoneal space, the fluid of the abdominal cavity. These nanoparticles gradually released the drug in high concentrations at the target site; however, the conventional nanoparticles get cleared from the target region very quickly, without inducing much therapeutic effect.

Consequently, the researchers developed nanoparticles covered with aldehyde groups that enabled them to chemically adhere to mesothelial cells in the abdominal cavity. When

tested on experimental models with human tumors growing in their abdominal regions, these bioadhesive nanoparticles were found to deliver EB precisely to its target sites and stayed in place for considerably longer duration (a minimum of 24 hours), compared to the non-adhesive nanoparticles that started leaving the abdominal cavity just after five minutes. Moreover, the researchers reported a remarkable improvement in survival among the experimental models; 60% of those treated with the bioadhesive nanoparticles survived for four months, compared to those in the control group, where 10% or fewer lived as long.

Localizing the delivery of the drug helped in reducing the toxicity of the drug, along with increasing its effectiveness. This novel treatment method seems particularly beneficial to patients with advanced stages of ovarian and uterine cancer, which due to its ominous spread in the peritoneal region, is very difficult to treat.

**Source:** Fighting cancer with sticky nanoparticles. Available at: <https://www.sciencedaily.com/releases/2016/09/160920103450.htm>. Accessed on 12.10.2016.



## CONFERENCE CALENDAR

January 27 – 30, 2017

### ECCO2017 — European Cancer Congress 2017

Amsterdam, The Netherlands  
<http://www.eccocongress.org/>

February 2 – 4, 2017

### EMBL-Cancer Core Europe Conference: Cancer Immunotherapy

Heidelberg, Germany  
<http://www.embl.de/training/events/2017/CCE17-01/index.html>

March 1 – 3, 2017

### AEK — 19<sup>th</sup> International AEK Cancer Congress

Heidelberg, Germany  
<http://www.aek-congress.org/>

April 20 – 22, 2017

### Cancer Metastasis — Cancer Metastasis through the Lymphovascular System: Biology & Treatment, 7<sup>th</sup> International Symposium

San Francisco, USA  
<http://cancermetastasis.org/>

May 12 – 15, 2017

### iwCLL — XVII International Workshop on Chronic Lymphocytic Leukemia

New York, USA  
<http://www.iwcll2017.org/>

June 2 – 6, 2017

### American Society of Clinical Oncology 2017 Annual Meeting

Chicago, USA  
<https://am.asco.org/past-and-future-meetings-1>

July 3 – 6, 2017

### 2<sup>nd</sup> DNA Replication as a Source of DNA Damage Conference

Rome, Italy  
<https://www.fusion-conferences.com/conference67.php>

September 8 – 12, 2017

### ESMO 2017 Congress

Madrid, Spain  
<http://www.esmo.org/Conferences/ESMO-2017-Congress>

**Durogesic®**

fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**

Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**

(Tramadol 37.5 mg + Paracetamol 325 mg)

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**Abbreviations:** IV - Intravenous; SC - Subcutaneous; w/ - With; w/o - Without; ↑ - Increase; ↓ - Decrease; Rx - Treatment;  
GI: Gastrointestinal; NSAIDs: Non-steroidal antiinflammatory drug(s); OD - Once daily; BID/BD - Twice daily; TID/TD - Thrice daily.

**INDICATIONS:** Safe - ✓      Caution - !      Contraindicated - x

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fentanyl transdermal system  
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## ► ALKYLATING AGENTS

ALTRETAMINE	 !  X  X	Alkylating agent
<p><b>INDICATION</b> Palliative treatment of persistent or recurrent ovarian cancer.</p> <p><b>MECHANISM OF ACTION</b> N-demethylation of altretamine may yield reactive intermediates that covalently bind to DNA, leading to DNA damage.</p> <p><b>DOSAGE</b> Adults (oral): 260 mg/m<sup>2</sup>/day in 4 divided doses, for 14-21 days of a 28-day cycle.</p>	<p><b>CONTRAINDICATIONS</b> Hypersensitivity, severe bone marrow suppression, severe neurologic toxicity.</p> <p><b>DRUG INTERACTIONS</b> Increases toxicity of amitriptyline, clomipramine and imipramine. Increased risk of orthostatic hypotension.</p>	<p><b>ADVERSE EFFECTS</b> Anemia, nausea, vomiting, peripheral and central neuropathies, thrombocytopenia.</p> <p><b>SPECIAL PRECAUTIONS</b> Perform peripheral blood counts and neurological examinations regularly before and after drug therapy.</p>

BUSULFAN	 !  X  X	Alkylating agent
<p><b>INDICATION</b> Palliation of chronic myelogenous leukemia (CML).</p> <p><b>MECHANISM OF ACTION</b> It has high specificity for myeloid elements and granulocyte precursors being most sensitive, followed by platelets and RBC.</p> <p><b>DOSAGE</b> Adults (Oral): Palliation of chronic myeloid leukemia: 60 mcg/kg/day. Maintenance dose: 0.5-2 mg/day. Max: 4 mg/day.</p> <p><b>CONTRAINDICATIONS</b> Known hypersensitivity. Doubtful CML diagnosis, chronic lymphocytic leukemia, acute leukemia and CML blast crises.</p>	<p><b>DRUG INTERACTIONS</b> Other myelosuppressives, especially, thioguanine: myelosuppression. Concurrent alkylating agents may cause hepatic venoocclusive disease.</p> <p><b>ADVERSE EFFECTS</b> Bone marrow failure, widespread epithelial (esp. bronchopulmonary) dysplasia with (esp. pulmonary and endocardial) fibrosis, chromosomal aberrations/mutations, malignancy, e.g. acute leukemia, ovarian suppression and amenorrhoea, life threatening hepatic venoocclusive disease, cardiac tamponade, hyperpigmentation, adrenal insufficiency, esophageal varices, hyperuricemia and hyperuricosuria.</p>	<p><b>SPECIAL PRECAUTIONS</b> Stop the drug when TLC <math>\leq</math> 15000/mm<sup>3</sup> (restart if <math>\geq</math> 50,000 mm<sup>3</sup>). Periodical complete blood counts mandatory. Advise patients to report if any adverse effects occur. Marrow compromise due to prior irradiation or chemotherapy.</p>

CARMUSTINE	 X  X  X	Alkylating agent
<p><b>INDICATIONS</b> Brain tumors, Hodgkin's and Non-Hodgkin's lymphoma.</p> <p><b>MECHANISM OF ACTION</b> Inhibits DNA synthesis and functioning.</p> <p><b>DOSAGE</b> Adult: 150-200 mg/m<sup>2</sup> via infusion as a single dose or divided into 2 doses and administered on 2 consecutive days. May repeat doses 6 weekly if tolerated.</p> <p><b>CONTRAINDICATIONS</b> Known hypersensitivity, pregnancy and lactation.</p>	<p><b>DRUG INTERACTIONS</b> Etoposide, mitomycin, phenytoin, radiation therapy, alcohol. Increased myelotoxicity when administered with cimetidine.</p> <p><b>ADVERSE EFFECTS</b> Gastrointestinal upset, anorexia, allergic reactions, irritation, pulmonary fibrosis, renal and hepatic damage, optic neuritis, convulsions, cerebral edema in patients given implants; wound-healing abnormalities, increased intracranial infection. Hyperpigmentation, hypotension, tachycardia. Alopecia; blood disorders; hyperprolactinemia and hypothyroidism in patients with brain tumors treated with radiation. Myelosuppression.</p>	<p><b>SPECIAL PRECAUTIONS</b> Children: Reduced lung function, renal or hepatic impairment, depressed platelet, leukocyte or erythrocyte counts, bone-marrow depression. Monitor blood counts, liver, renal and pulmonary function before and regularly during treatment.</p>

**CHLORAMBUCIL**

Alkylating agent

**INDICATIONS**

Chronic lymphocytic leukemia, certain forms of Non-Hodgkin's lymphomas, Hodgkin's disease, Waldenstrom's macroglobulinemia, ovarian adenocarcinoma and breast cancer.

**MECHANISM OF ACTION**

It causes cell cycle arrest at G2 stage by causing cross linking of cellular DNA strands. DNA breaks down and cell dies.

**DOSAGE**

Adult: Oral: *Hodgkin's disease*: 200 mcg/kg/day. Maintenance dose:

30-100 mcg/kg/day. *Non-Hodgkin's lymphoma*: 100 mcg/kg/day. Maintenance dose: 30-100 mcg/kg/day. *Chronic lymphocytic leukemia*: 100-200 mcg/kg/day for 3-8 week. Maintenance dose: 30-100 mcg/kg/day. *Waldenstrom's macroglobulinemia*: Starting dose: 6-12 mg/day until leucopenia develops. Maintenance dose: 2-8 mg/day.

**CONTRAINDICATIONS**

Hypersensitivity, demonstrated resistance to the agent.

**DRUG INTERACTIONS**

↑ effect of other myelosuppressive

agents, impaired immune response to vaccines.

**ADVERSE EFFECTS**

Skin rash, amenorrhea, bone marrow suppression (most common) normally reversible, oral ulceration, CNS disturbances, GI upsets, vomiting, seizures, hepatotoxicity, azoospermia, pulmonary fibrosis.

**SPECIAL PRECAUTIONS**

Stop the treatment if leucocyte or platelet counts fall below normal. Use cautiously in history of seizures and head injury.

**CYCLOPHOSPHAMIDE**

Alkylating agent

**INDICATIONS**

Malignant lymphomas, multiple myeloma, leukemias (except blast crises), neuroblastoma, ovarian adenocarcinoma, retinoblastoma and breast carcinoma.

**MECHANISM OF ACTION**

It acts by alkylating DNA and causing cross linkage of DNA strands.

**DOSAGE**

Adult: Oral: *Malignancies*: Low-dose therapy: 2-6 mg/kg weekly in divided dose. Intravenous: Moderate dose therapy: 10-15 mg/kg weekly; high dose therapy: 20-40 mg/kg every 10-20 days. Dosage individualized according to disease state, patient's condition,

bone marrow status and whether it is used as a single agent or in combination regimens.

**CONTRAINDICATIONS**

Severe marrow depression, previous hypersensitivity.

**DRUG INTERACTIONS**

Allupurinol causes ↑ in cyclophosphamide toxic effects. High dose phenobarbitone causes ↑ in cyclophosphamide metabolism and leukopenic activity. Cytotoxic drugs: additive cytotoxicity. Succinyl choline causes ↑ anticholinesterase actions. Doxorubicin causes ↑ in cyclophosphamide cardiotoxicity.

**ADVERSE EFFECTS**

Nausea/vomiting, hair loss, irregular menstruation, mouth ulcers, hemorrhagic cystitis, blood dyscrasias (cytotoxicity), carcinogenesis (e.g. bladder, blood, breast), pulmonary fibrosis, infections and sterility.

**SPECIAL PRECAUTIONS**

Use cautiously in decreased blood counts, marrow infiltration or irradiation, hepatic/renal/adrenal impairment. Reduced dose necessary in children. It may cause birth defects. The drug passes into breastmilk and may affect the infant adversely.

**IFOSFAMIDE**

Alkylating agent

**INDICATIONS**

Solid tumors: those of the cervix, endometrium, lung, ovary, testis, thymus, sarcomas, including osteosarcoma, rhabdomyosarcomas, Burkitt's lymphoma (as an alternative to cyclophosphamide).

**MECHANISM OF ACTION**

It causes cell cycle arrest at G2 stage by causing cross linking of cellular DNA strands. DNA breaks down and cell dies.

**DOSAGE**

Adult: IV: *Lymphoma*; *Sarcoma*; *Solid tumors*: Variable dosing regimens available. 8-12 g/m<sup>2</sup>

divided over 3-5 days, repeat course 2-4 weekly.

**CONTRAINDICATIONS**

Severe marrow suppression, previous hypersensitivity, acute UTI, vesical bleed.

**DRUG INTERACTIONS**

Oral anticoagulants (warfarin) cause ↑ anticoagulant effect. Cisplatin: Induced ototoxicity/nephrotoxicity is ↑.

**ADVERSE EFFECTS**

Urothelial toxicity: Proximal/distal tubular damage, glomerular damage, vesical damage, Fanconi's syndrome, dangerous

hypokalemia, myocardial depression, VPCs, heart failure, encephalopathy, EEG abnormality, disorientation, catatonia and coma.

**SPECIAL PRECAUTIONS**

Use cautiously in cardiac/hepatic/renal/CNS impairment. Stop treatment if TLC drops below, say 3000/mm<sup>3</sup>. Wear latex (rather than PVC) gloves while handling ifosfamide and change them at least every 2 hrs. Dose according to body surface area (m<sup>2</sup>) in children. CNS, CVS, renal and other vital organ functions is to be kept in mind when prescribing in elderly.

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12 mcg/hr, 25 mcg/hr, 50 mcg/hr

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Tramadol 37.5 mg + Paracetamol 325 mg

**LOMUSTINE**

Alkylating agent

**INDICATIONS**

Brain tumor, Hodgkin's disease, lung cancer, malignant melanoma.

**MECHANISM OF ACTION**

It is a lipid soluble alkylating agent with a wide range of anti-tumor activity. It also crosses blood brain barrier.

**DOSAGE**

Adults: Oral 100-130 mg/m<sup>2</sup> as a single dose every 6 weeks. Adjusted according to platelet and leucocyte

counts. Compromised marrow function: 100 mg/m<sup>2</sup> as single dose every 6 weeks. Children: Oral 75-150 mg/m<sup>2</sup> as single dose every 6 weeks. Readjust dose according to platelet and leucocyte counts.

**CONTRAINDICATION**

Hypersensitivity.

**DRUG INTERACTIONS**

Theophylline causes leucopenia, thrombocytopenia.

**ADVERSE EFFECTS**

Bone marrow suppression, nephrotoxicity, nausea/ vomiting, pulmonary fibrosis, raised liver enzymes, stomatitis and alopecia.

**SPECIAL PRECAUTIONS**

Monitor blood counts regularly. Use cautiously in renal impairment. The dose to be repeated only after 6 weeks. Not recommended in infants. Increased risk of adverse effects in elderly. It causes fetal harm.

**CHLORMETHINE**

Alkylating agent

**INDICATIONS**

Advanced Hodgkin's lymphoma and intracavitary malignant effusions.

**MECHANISM OF ACTION**

Forms DNA cross-links, resulting in inhibition of DNA synthesis and function.

**DOSAGE**

Adults: Advanced Hodgkin's Lymphoma: 400 mcg/kg as a single dose or in divided doses on successive days. Intracavitary Malignant effusions: 0.2-0.4 mg/kg as a single dose.

Repeat if needed.

**CONTRAINDICATIONS**

Severe myelosuppression or infection, known hypersensitivity, pregnancy and lactation.

**DRUG INTERACTIONS**

Alcohol, altered response to vaccines.

**ADVERSE EFFECTS**

Myelosuppression, GI disturbances, anorexia, metallic taste, tinnitus, vertigo, deafness, headache, drowsiness, fever, neurological symptoms, jaundice,

maculopapular rashes, severe irritation due to extravasation, impaired spermatogenesis, temporary or permanent inhibition of fertility, strong vesicant action, menstrual disturbances, precipitation of herpes zoster, alopecia and hyperuricemia.

**SPECIAL PRECAUTIONS**

Concurrent radiotherapy; secondary leukemia. Monitor hepatic, renal and bone marrow function. Avoid contact with skin and mucous membranes due to strong vesicant action.

**MELPHALAN**

Alkylating agent

**INDICATIONS**

Multiple myeloma, advanced epithelial ovarian carcinoma, breast carcinoma, malignant melanoma and polycythemia vera.

**MECHANISM OF ACTION**

It is effective in multiple myeloma and other malignancies and also active against both resting and dividing cells.

**DOSAGE**

Adult: Oral: *Multiple myeloma*: 150 mcg/kg/day in divided doses for 4-7 days rest period (for hematologic recovery) up to 6 week, then repeat the course or start maintenance dose 1-3 mg/day. *Breast cancer*: 150 mcg/kg/day, repeat 6 weekly. *Ovarian carcinoma*: 200 mcg/kg/day

for 5 days 4-8 weekly. *Polycythemia vera*: 10-10 mg/day for 5-7 days; 2-4 mg/day for remission induction. Maintenance dose: 2-6 mg/week. IV: *Ovarian adenocarcinoma*: 1 mg/kg as a single dose, repeat in 4 weeks if platelet and neutrophil counts under control. *Multiple myeloma*: 400 mcg/kg/m<sup>2</sup> via infusion, 1st 4 doses may be given 2 weekly; further doses administered 4 weekly depending on toxicity.

**CONTRAINDICATIONS**

Hypersensitivity, pregnancy.

**DRUG INTERACTIONS**

Concurrent nalidixic acid causes fatal reaction in children. Cyclosporine causes risk of renal

damage. Prednisolone causes antineoplastic effect.

**ADVERSE EFFECTS**

Inappropriate secretion of ADH, amenorrhea, oral ulceration, pulmonary fibrosis, GI upsets, bone marrow depression, thrombocytopenia, leukemia, sterility, allergic reactions, leukemogenicity, mutagenicity.

**SPECIAL PRECAUTIONS**

The drug is stopped if the leukocyte count falls below 3000/mm<sup>3</sup> or platelets below 100000/mm<sup>3</sup>. Contraindicated in infants as safety not established. It may cause increased adverse effects in elderly. Lactation.

TEMZOLOMIDE	! @ x !	Alkylating agent
<b>INDICATIONS</b>		(DTIC) or pregnancy.
Glioblastoma multiforme and metastatic melanoma.		<b>DRUG INTERACTIONS</b>
<b>MECHANISM OF ACTION</b>		Administration of valproic acid decreases oral clearance of temozolamide by about 5%.
Temozolamide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyl-triazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.		<b>ADVERSE EFFECTS</b>
<b>DOSAGE</b>		Alopecia, fatigue, nausea, vomiting, anorexia, headache, constipation, convulsions and thrombocytopenia.
Adult: Oral: <i>Glioblastoma multiforme:</i> Concomitant phase:		<b>SPECIAL PRECAUTIONS</b>
75 mg/m <sup>2</sup> once daily for 42 days with focal radiotherapy. Initiate monotherapy 4 weeks after completing concomitant phase: 150 mg/m <sup>2</sup> once daily for 5 days followed by a 23 day break (1 cycle). Cycle 2: 200 mg/m <sup>2</sup> once daily for 5 days. If dose cannot be increased in cycle 2, do not increase dose in subsequent cycles. Dose used in cycle 2 is administered for remaining cycles, toxicity allowing, up to 6 cycles.		Hepatitis screening and prophylactic therapy with antiviral agents as clinically indicated should be considered in patients receiving temozolamide.
<b>CONTRAINDICATIONS</b>		
Known hypersensitivity to temozolamide or any ingredient in the formulation. Known hypersensitivity to dacarbazine		

THIOTEP A	! @ x ! x	Alkylating agent
<b>INDICATIONS</b>		<b>ADVERSE EFFECTS</b>
Bladder cancer, ovarian cancer, breast cancer, malignant effusions and condylomata acuminata.		Bone marrow depression, mutagenesis, teratogenesis and carcinogenesis are the most severe adverse effects of thiotepa therapy. Others are GI disturbances; fatigue, weakness, headache and dizziness; hypersensitivity reactions; blurred vision and conjunctivitis, amenorrhea, impaired fertility, local irritation, frank chemical or hemorrhagic cystitis, depigmentation of periorbital skin (eye drops).
<b>MECHANISM OF ACTION</b>		<b>CONTRAINDICATIONS</b>
Being an ethylenimine alkylating agent, thiotepa disrupts the bond of DNA and interferes with DNA replication, protein synthesis, and transcription of RNA. This finally results in the disruption of nucleic acid function. The principal bond disruption by thiotepa is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar that liberates alkylated guanines.		Hypersensitivity, severe myelosuppression with leukocyte count <3000 cells/mm <sup>3</sup> or platelet count <150,000 cells/mm <sup>3</sup> . Pregnancy and lactation.
<b>DOSAGE</b>		<b>DRUG INTERACTIONS</b>
Adult: IV: <i>Bladder cancer:</i> Instill ≤60 mg into the bladder of patient previously dehydrated for 8-12 hr and retained for 2 hr. May repeat weekly, for up to 4 week. <i>Breast cancer; ovarian carcinoma:</i> Dosage must be individualized. Dosing Range: 0.3-0.4 mg/kg 1-4 weekly. <i>Urethral condylomata acuminata:</i> Instill 60 mg/week into urethra. <i>Intracavitory malignant effusions:</i> Up to 60 mg in 20-60 mL of sterile water may be instilled after aspiration.		
<i>Thiotepa may decrease the metabolism and clearance of CYP2B6 inhibitor agents like cyclophosphamide, bupropion, promethazine, selegiline. Simultaneous administration of other alkylating agents or irradiation enhances effect. Thiotepa inhibits the plasma pseudocholinesterase and prolongs the action of succinylcholine and other neuromuscular-blocking agents. Thiotepa must be used either 24 hr before or 24 hr after administration of cytotoxic chemotherapy to avoid the risk of myelosuppression when used with colony-stimulating factors (such as filgrastim, lenograstim). Thiotepa decreases effects of adenovirus types 4 and 7 by pharmacodynamic antagonism.</i>		<b>SPECIAL POPULATION</b>
		Use cautiously in renal, hepatic and bone marrow function impairment. Patient should be cautious for secondary malignancies which are potentially carcinogenic. The patient should monitor his blood counts before initiation at least weekly during treatment and 3 weeks after discontinuation of therapy.

## ► NON-CLASSIC ALKYLATING AGENTS

DACARBAZINE		Non-classic alkylating agent
<b>INDICATIONS</b> Metastatic malignant melanoma, Hodgkin's disease and soft tissue sarcomas.	<b>disease:</b> 150 mg/m <sup>2</sup> /day - 5 days. The treatment may be repeated after 4 weeks.	rashes, photosensitivity, nausea/vomiting, diarrhea, fever, myalgia, alopecia and flushing.
<b>MECHANISM OF ACTION</b> It causes cell cycle arrest at G2 stage by causing cross linking of cellular DNA strands. DNA breaks down and cell dies.	<b>CONTRAINdications</b> Hypersensitivity, severe myelosuppression.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in hepatic and renal impairment. Fasting 4-6 hrs prior to the treatment. Avoid skin and eye contact. Maintain blood counts. Reduced dose necessary in elderly and children. Possibly teratogenic.
<b>DOSAGE</b> <i>Malignant melanoma:</i> 2 - 4.5 mg/kg/day - 10 days. The treatment may be repeated after 4 weeks. <i>Hodgkin's</i>	<b>DRUG INTERACTIONS</b> Effect of other myelosuppressive agents.	<b>ADVERSE EFFECTS</b> Bone marrow depression (most common), facial paresthesias,

PROCARBAZINE		Non-classic alkylating agent
<b>INDICATION</b> For use in combination with other anticancer drugs for the treatment of stage III and IV Hodgkin's disease.	<b>DOSAGE</b> Adult: Oral Monotherapy: Start at 50 mg/day; increase gradually if needed. Maintenance dose: 50-150 mg/day until a cumulative dose of at least 6 grams. Combination Therapy: 100 mg/m <sup>2</sup> on days 1-14 of each 4 or 6-week cycle.	Phenylbutazone and warfarin. ↑ the effect of chlorambucil.
<b>MECHANISM OF ACTION</b> It causes cell cycle arrest at G2 stage by causing cross linking of cellular DNA strands. DNA breaks down and cell dies. In addition, procarbazine may directly damage DNA. Hydrogen peroxide, formed during the auto-oxidation of the drug, may attack protein sulfhydryl groups contained in residual protein which is tightly bound to DNA.	<b>CONTRAINDICATION</b> Hypersensitivity, severe myelosuppression, pregnancy and lactation.	<b>ADVERSE EFFECTS</b> Bone marrow depression (most common), facial paresthesias, rashes, photosensitivity, nausea/vomiting, diarrhea, fever, myalgia, alopecia and flushing.
	<b>DRUG INTERACTIONS</b> ↑ effect of other myelosuppressive agents.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in renal and/or hepatic impairment. Possibly teratogenic. Radiation or a chemotherapeutic agent known to have marrow-depressant activity.



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(Tramadol 37.5 mg + Paracetamol 325 mg)

## ► PLATINUM ANALOGS

CARBOPLATIN	 !  X 	Platinum analog
<p><b>INDICATION</b> Advanced ovarian carcinoma.</p> <p><b>MECHANISM OF ACTION</b> It causes cross-linking of DNA strands.</p> <p><b>DOSAGE</b> Adult: Intravenous single agent in treatment-naïve patients: 400 mg/m<sup>2</sup>; As single agent in previously treated patients: 360 mg/m<sup>2</sup>; with cyclophosphamide in treatment-naïve patients: 300 mg/m<sup>2</sup>. Dose to be administered 4 weekly.</p>	<p>Subsequent dose adjustment based on hematological counts.</p> <p><b>CONTRAINDICATIONS</b> Hypersensitivity to platinum compounds, e.g. cisplatin. Severe bone marrow depression, severe bleeding.</p> <p><b>DRUG INTERACTIONS</b> ↑ nephrotoxicity with nephrotoxic drugs</p> <p><b>ADVERSE EFFECTS</b> Bone marrow suppression, allergic reaction, pain, asthenia, alopecia,</p>	<p>nausea/vomiting, peripheral neuropathy, nephrotoxicity, hepatotoxicity, ototoxicity, electrolyte imbalance.</p> <p><b>SPECIAL PRECAUTIONS</b> Use cautiously in hepatic and renal dysfunction. Avoid contact of the drug with aluminium. Increased adverse effects in elderly cause fetal harm. Alcohol may cause increased adverse effects.</p>

CISPLATIN	 !  X 	Platinum analog
<p><b>INDICATIONS</b> Metastatic testicular tumors, metastatic ovarian tumors and advanced bladder cancer.</p> <p><b>MECHANISM OF ACTION</b> It modifies cell cycle by interfering with DNA structure and function, especially during the S-phase but cells are killed at all stages.</p> <p><b>DOSAGE</b> Adult: IV: <i>Metastatic testicular tumors</i>: 20 mg/m<sup>2</sup>/day for 5 days per cycle. <i>Metastatic ovarian tumors</i>: In monotherapy: 100 mg/m<sup>2</sup> per cycle- as single dose once every 4 week. In combination therapy with cyclophosphamide:</p>	<p>75-100 mg/m<sup>2</sup> on day 1 of every 4-weeks cycle. <i>Advanced bladder cancer</i>: 50-70 mg/m<sup>2</sup> per cycle once every 3-4 weeks.</p> <p><b>CONTRAINDICATIONS</b> Hypersensitivity to cisplatin or other platinum drugs, severe renal impairment, myelosuppression, hearing impairment, pregnancy and lactation.</p> <p><b>DRUG INTERACTIONS</b> Cisplatin is given only under close medical supervision, interactions with cisplatin are carefully monitored and the dosage is adjusted accordingly. ↓ serum anticonvulsant levels, when used</p>	<p>along with cisplatin. Action duration of cisplatin affected by concomitant pyridoxine administration.</p> <p><b>ADVERSE EFFECTS</b> Nausea/vomiting, loss of appetite/taste, ringing in the ears/hearing loss, breathing difficulties, fits, wheezing and swollen face/rash.</p> <p><b>SPECIAL PRECAUTIONS</b> The drug passes into breastmilk and may affect the infant adversely. Cisplatin may cause birth defects or premature birth. Reduced doses may be necessary in elderly as increased likelihood of adverse effects.</p>

OXALIPLATIN	 X  X 	Platinum analog
<p><b>INDICATIONS</b> Adjuvant treatment of stage III colon cancer and advanced colorectal cancer.</p> <p><b>MECHANISM OF ACTION</b> Oxaliplatin, a platinum derivative, is an alkylating agent. Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.</p>	<p><b>DOSAGE</b> Adult: IV: <i>Adjuvant therapy in Stage III colon cancer</i>: 85 mg/m<sup>2</sup> every 2 weeks - 12 cycles. After recovery from toxicity, reduce dose to 65 mg/m<sup>2</sup>. Administer before fluoropyrimidines. <i>Advanced colorectal cancer with fluorouracil and folinic acid</i>: 85 mg/m<sup>2</sup> every 2 weeks. After recovery from toxicity reduce to 65 mg/m<sup>2</sup>. Administer before fluoropyrimidines.</p>	<p><b>CONTRAINDICATIONS</b> Hypersensitivity to oxaliplatin, other platinum-containing compounds, or any component of the formulation.</p> <p><b>DRUG INTERACTIONS</b> When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin, oxaliplatin) to limit myelosuppression and enhance efficacy. It may decrease plasma levels of digoxin.</p>

## ► ANTIMETABOLITES &gt; ANTIFOLATES

METHOTREXATE		Antifolate
<p><b>INDICATIONS</b></p> <p>Burkitt's lymphoma, breast cancer, choriocarcinoma, osteosarcoma, advanced lymphosarcoma and acute lymphoblastic leukemia.</p> <p><b>MECHANISM OF ACTION</b></p> <p>It inhibits dihydrofolate reductase (DHFRase) and blocks conversion of dihydrofolate acid (DHFA) to tetrahydrofolic acid (THFA) which is an essential coenzyme required for one carbon transfer reaction in purine synthesis and amino acid interconversion.</p> <p><b>DOSAGE</b></p> <p>Adult: Oral: <i>Burkitt's lymphoma:</i> 10-25 mg/day for 4-8 days, repeat after 7-10 days. <i>Breast cancer:</i> 10-60 mg/m<sup>2</sup> often with cyclophosphamide and fluorouracil. <i>Choriocarcinoma:</i> 15-30 mg/day for 5 days, repeat after an interval of at least 1 week for</p>	<p>3-5 courses. <i>Osteosarcoma:</i> 12-15 g/m<sup>2</sup> as infusion, followed by folic acid. <i>Advanced lymphosarcoma:</i> Up to 30 mg/kg, followed by folic acid rescue. <i>Acute lymphoblastic leukemia:</i> Maintenance: 2.5 mg/kg every 14 days.</p> <p><b>CONTRAINDICATIONS</b></p> <p>Chronic liver disease, hypersensitivity, immunodeficiency, hematological disorders, renal impairment. Pregnancy. Lactation.</p> <p><b>DRUG INTERACTIONS</b></p> <p>NSAIDs: Increased toxicity. Cisplatin: Causes nephrotoxicity. Oral antibiotics, e.g. tetracycline, chloramphenicol, other broad spectrum antibiotics: ↓ methotrexate absorption. Penicillin cause ↓ in renal methotrexate clearance and increased toxicity. Folic acid and its derivatives cause ↓ in methotrexate efficacy.</p>	<p><b>ADVERSE EFFECTS</b></p> <p>GI upsets, anaphylaxis, hepatic necrosis, marrow depression, menstrual dysfunction, renal toxicity, fever and chills, decreased resistance, oral inflammation and rashes.</p> <p><b>SPECIAL PRECAUTIONS</b></p> <p>Use cautiously in active infection, debilitated patients, pleural effusion, ascites. Avoid immunization during Rx. Use only in cancer treatment in children. Alcohol may add to the hepatotoxicity of methotrexate. May cause an increase in adverse effects in elderly.</p>
<p><b>PEMETREXED</b></p> <p><b>INDICATIONS</b></p> <p>Malignant pleural mesothelioma, non-small cell lung cancer.</p> <p><b>MECHANISM OF ACTION</b></p> <p>Pemetrexed, a folic acid antagonist, exerts its antineoplastic activity by disrupting folate-dependent metabolic processes that are essential for cell replication. Pemetrexed inhibits the folate-dependent enzymes thymidylate synthase, dihydrofolate reductase, and phosphoribosylglycinamide formyltransferase (glycinamide ribonucleotide formyltransferase), enzymes involved in <i>de novo</i> biosynthesis of thymidine and purine nucleotides.</p>	<p><b>DOSAGE</b></p> <p><i>Malignant pleural mesothelioma:</i> 500 mg/m<sup>2</sup> infused IV over 10 minutes in conjunction with cisplatin infused IV over 2 hours beginning approximately 30 minutes after completion of the pemetrexed infusion on day 1 of a 21-day cycle. <i>Non-small cell lung cancer:</i> 500 mg/m<sup>2</sup> infused IV over 10 minutes on day 1 of a 21-day cycle.</p> <p><b>CONTRAINDICATIONS</b></p> <p>Known hypersensitivity to pemetrexed or any ingredient in the formulation.</p> <p><b>DRUG INTERACTIONS</b></p> <p>NSAIDs can ↓ the elimination</p>	<p>of pemetrexed. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed.</p> <p><b>ADVERSE EFFECTS</b></p> <p>Hematological side-effects, fever and infection, stomatitis/pharyngitis, rash/desquamation, nausea, fatigue, dyspnea, vomiting, constipation, chest pain, and anorexia.</p> <p><b>SPECIAL PRECAUTIONS</b></p> <p>Complete blood cell counts, including platelet counts, should be performed in all patients receiving pemetrexed. Renal and hepatic function should be monitored periodically.</p>

► ANTIMETABOLITES > FLUOROPYRIMIDINES

5-FLUOROURACIL		Fluoropyrimidine
<b>INDICATIONS</b>		
Palliative treatment of carcinoma of colon, rectum, breast, stomach and pancreas.		
<b>MECHANISM OF ACTION</b>		
The active metabolite causes inhibition of thymidylate synthase and blocks the conversion of deoxyuridic acid to deoxythymidylic acid and selective failure of DNA synthesis occurs.		
<b>DOSAGE</b>		
Adult: Oral: <i>Palliation of malignant neoplasms:</i> 15 mg/kg, may be given once weekly for maintenance. Maximum dose: 1 g/day. Intravenous: <i>Palliation of malignant neoplasms:</i> 12 mg/kg/day (max: 0.8-1g/day) for 3-4 days.	In case no toxicity occurs, may be followed after 1 day with 6 mg/kg on alternate days for another 3-4 doses. Repeat course 4-6 week later or maintenance therapy of 5-15 mg/kg (max: 1 g) may be given weekly.	disorientation, thrombophlebitis, nail changes, hand-foot syndrome, nausea/vomiting, diarrhea, anorexia, oral inflammation and ulceration, hematological disturbances and GI ulceration.
<b>CONTRAINDICATIONS</b>		
Hypersensitivity, bone marrow suppression, poor nutritional state, serious infections. Pregnancy. Lactation.		
<b>DRUG INTERACTIONS</b>		
Leucovorin calcium may enhance fluorouracil toxicity.		
<b>ADVERSE EFFECTS</b>		
Leukopenia, rashes, CNS disturbances, photosensitivity, pigmentation,		SPECIAL PRECAUTIONS
		Close monitoring during the treatment. Use cautiously in hepatic and renal impairment and stomatitis. The treatment to be stopped if signs of toxicity occur. Safety and effectiveness in children not established. It may affect nursing infants and cause teratogenesis. Alcohol may lead to increased adverse effects. e.g. WBC <3500/mm <sup>3</sup> or platelets <1,00,000/mm <sup>3</sup> .

CAPECITABINE		Fluoropyrimidine
<b>INDICATIONS</b>		
Colorectal cancer and breast cancer.		
<b>MECHANISM OF ACTION</b>		
Capecitabine is selectively converted by tumor cells to active metabolite 5-fluorouracil (5-FU). Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). The main mechanism is thought to be the binding of the deoxyribonucleotide of the drug (FdUMP) and the folate cofactor (N5-10-methylenetetrahydrofolate) to thymidylate synthase (TS) to form a covalently bound ternary complex, which inhibits the formation of thymidylate from 2'-deoxyuridylate, thereby interfering with DNA synthesis. In addition, FUTP can be incorporated into RNA in place of uridine triphosphate (UTP), producing a fraudulent RNA and	interfering with RNA processing and protein synthesis.	<b>ADVERSE EFFECTS</b>
		Diarrhea, nausea, vomiting, stomatitis, abdominal pain, dyspepsia, constipation, hand-and-foot syndrome, erythema, rash, alopecia, pyrexia, headache, dizziness, anorexia, epistaxis, dyspnea and cough.
<b>DOSAGE</b>		
Adult: Oral <i>Colorectal cancer and breast cancer:</i> 1250 mg/m <sup>2</sup> twice daily for 14 days followed by a 7-day rest period. Treatment duration for colorectal cancer: 6 months.		<b>SPECIAL PRECAUTIONS</b>
		Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when capecitabine is administered. If grade 2 or 3 hand-and-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Population with age >60 are at higher risk for adverse effects and coagulopathy.
<b>CONTRAINDICATIONS</b>		
Known hypersensitivity to capecitabine, known hypersensitivity to 5-FU, known dihydropyrimidine dehydrogenase (DPD) deficiency, severe renal impairment (creatinine clearance below 30 mL/min).		
<b>DRUG INTERACTIONS</b>		
Capecitabine and/or its metabolites inhibit the metabolism of warfarin. Concomitant use of phenytoin and capecitabine may result in toxicity from increased serum phenytoin concentrations.		

## ► ANTIMETABOLITES &gt; DEOXYCYTIDINE ANALOGS

## CYTARABINE



Deoxycytidine analog

**INDICATIONS**

High dose cytarabine therapy in patients with: refractory acute non-lymphoblastic leukemias (ANLL) refractory acute lymphoblastic leukemias (ALL), blast crisis of chronic myeloid leukemia (CML). High risk leukemias such as i) acute leukemias as secondary malignancies after preceding chemotherapy and/or radiation and ii) transformation of preleukemias and refractory Non-Hodgkin's lymphomas.

**MECHANISM OF ACTION**

Cytarabine is an antimetabolite and inhibits the formation of deoxycytidine triphosphate, and thus DNA synthesis, by blocking the

reduction of cytidine phosphate to deoxycytidine phosphate.

**DOSAGE**

Adult: Intravenous/subcutaneous *Induction and maintenance of remission in acute leukemias:* IV 100 mg/m<sup>2</sup> twice-daily or 100 mg/m<sup>2</sup>/day continuous IV infusion for 5-10 days. Maintenance dose: 1-1.5 mg/kg 1-2 times/week IV/SC administration. Refractory disease: IV infusion of up to 3 g/m<sup>2</sup> 12 hourly for up to 6 days.

**CONTRAINDICATION**

Hypersensitivity.

**DRUG INTERACTIONS**

Digoxin: ↓ plasma digoxin levels. Gentamicin: ↓ gentamicin efficacy.

**ADVERSE EFFECTS**

Bone marrow suppression causing leukopenia, thrombocytopenia, hepatic dysfunction, bleeding, Infection, conjunctivitis, CNS toxicity, anorexia, nausea/vomiting, diarrhea, oral ulceration, fever, abdominal rash.

**SPECIAL PRECAUTIONS**

Blood counts to be monitored daily during the treatment. Bone marrow examination to be done regularly. Indicated in certain leukemias, under strict supervision in children. Increased risk of adverse effects in elderly. It causes fetal harm.

## GEMCITABINE



Deoxycytidine analog

**INDICATIONS**

Locally advanced non-small cell lung cancer, locally advanced (non-resectable stage II/III)/metastatic (stage IV) adenocarcinoma pancreas, including 5-FU-refractory pancreatic carcinoma, advanced breast cancer, advanced ovarian cancer, advanced prostate cancer, advanced renal cancer, advanced bladder cancer.

**MECHANISM OF ACTION**

It kills cells undergoing DNA synthesis as well as blocks the progression of cells through the G1/S phase boundary. Blocks DNA synthesis.

**DOSAGE**

Adult: IV: *Advanced non-small cell lung cancer:* 1 g/m<sup>2</sup> on days 1, 8 and 15 of each 28-day cycle. *Pancreatic cancer:* 1 g/m<sup>2</sup> once weekly for up

to 7 week followed by rest of 1 week. Continue with once weekly infusions for 3 consecutive weeks out of 4. *Bladder cancer:* 1 g/m<sup>2</sup> on days 1, 8 and 15 of each 28-day cycle. Administer before cisplatin. *Breast cancer:* 1.25 g/m<sup>2</sup> on days 1 and 8 of each 21-day cycle. *Ovarian cancer:* 1 g/m<sup>2</sup> on days 1 and 8 of each 21-day cycle. Administer before carboplatin.

**CONTRAINDICATIONS**

Known hypersensitivity to the drug. Pregnancy. Lactation.

**DRUG INTERACTIONS**

May increase anti-coagulant effect of warfarin. Large volume, radiotherapy: severe esophagitis, pneumonitis.

**ADVERSE EFFECTS**

Flu-like syndrome, peripheral/generalized pulmonary edema,

alopecia, somnolence, nausea/vomiting, diarrhea/constipation, stomatitis, rash/pruritis/desquamation/ulceration, bronchospasm, anaphylaxis, suppressed marrow/blood indices (especially granulocytes), ↓ platelets.

**SPECIAL PRECAUTIONS**

Monitor blood indices, kidney function test and liver function test during therapy. Exercise caution in activity requiring skill/alertness. Use cautiously in liver/renal impairment. No specific dosage adjustment needed in elderly despite increased risk of reduced blood counts (esp in women). Not known whether human milk contains the drug. Do not refrigerate reconstituted drug solutions for fear of crystallization.

► ANTIMETABOLITES > PURINE AND PURINE ANTIMETABOLITES

6-MERCAPTOPURINE		Purine and purine antimetabolite
<b>INDICATIONS</b> Acute lymphatic leukemia (lymphocytic, lymphoblastic).	maintenance dose: Initial: 1.5-2.5 mg/kg/day, may carefully increased up to 5 mg/kg/day.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in chronic hepatic or renal disease, gout, recent infection and in other medications. Reduced dose necessary in elderly and children. The drug passes into breastmilk and may affect the infant adversely. Alcohol may increase the adverse effects of this drug.
<b>MECHANISM OF ACTION</b> It is converted in body to monoribonucleotide which inhibits the conversion of inosine monophosphate (IMP) to adenosine monophosphate (AMP)/guanosine monophosphate (GMP). This also causes feed back inhibition of <i>de novo</i> purine synthesis.	<b>CONTRAINDICATIONS</b> History of prior resistance to this drug, contraindicated unless the condition has been diagnosed clearly.	<b>DRUG INTERACTIONS</b> Allopurinol increases effect of mercaptopurine. Causes ↓ in warfarin effects.
<b>DOSAGE</b> The dose is usually individualized according to body weight and response. Adult: Oral: <i>Acute lymphatic leukemia:</i> Usual	<b>ADVERSE EFFECTS</b> Nausea/vomiting, loss of appetite, mouth ulcers, jaundice, melena, blood stained vomiting.	

6-THIOGUANINE		Purine and purine antimetabolite
<b>INDICATIONS</b> Acute lymphatic leukemia (lymphocytic, lymphoblastic), acute myelogenous leukemia (and acute myelomonocytic leukemia).	<b>CONTRAINDICATIONS</b> History of prior resistance to this drug, contraindicated unless the condition has been diagnosed clearly.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in chronic hepatic or renal disease, recent infection and with other medications. Reduced dose necessary in elderly and children. The drug passes into breastmilk and may affect the infant adversely. Alcohol may increase the adverse effects of this drug.
<b>MECHANISM OF ACTION</b> It is converted in body to monoribonucleotide which inhibits the conversion of IMP to AMP/GMP. This also causes feedback inhibition of <i>de novo</i> purine synthesis.	<b>DRUG INTERACTIONS</b> There is usually complete cross-resistance between mercaptopurine and thioguanine.	<b>ADVERSE EFFECTS</b> Nausea/vomiting, loss of appetite, mouth ulcers, jaundice, melena, blood stained vomit.
<b>DOSAGE</b> The dosage is determined individually according to body weight and response.		

CLADRIBINE		Purine and purine antimetabolite
<b>INDICATIONS</b> Hairy cell leukemia, chronic lymphocytic leukemia, refractory low-grade Non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia.	5 consecutive days of a 28-day cycle. Max: limit to 6 cycles.	disturbance, weakness, coughing, dyspnea, diaphoresis, trunk pain, serious neurotoxicity.
<b>MECHANISM OF ACTION</b> Inhibition of DNA synthesis and chain termination.	<b>CONTRAINDICATIONS</b> Pregnancy, lactation, and known hypersensitivity to ingredient.	<b>SPECIAL PRECAUTIONS</b> Monitor complete blood counts, liver function and hepatic function periodically. Use with caution in patients with preexisting hematologic or immunologic abnormalities.
<b>DOSAGE</b> Adult: <i>Hairy-cell leukemia:</i> IV dose of 90 mcg/kg/day for 7 consecutive days. <i>Chronic lymphocytic leukemia:</i> IV dose of 120 mcg/kg/day for	<b>DRUG INTERACTIONS</b> Alcohol, immunosuppressive or myelosuppressive therapy.	<b>ADVERSE EFFECTS</b> Myelosuppression, immuno-suppression, fever, fatigue, nausea, vomiting, rash, headache, GI

**FLUDARABINE**

Purine and purine antimetabolite

**INDICATIONS**

Treatment of patients with chronic lymphocytic leukemia (CLL) with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one alkylating agent containing regimen.

**MECHANISM OF ACTION**

It acts as cytotoxic chemotherapeutic agent.

**DOSAGE**

Adults: IV: 25 mg/m<sup>2</sup>/day for 5 consecutive days in every 28 days up to 6 weeks.

**CONTRAINDICATIONS**

Hypersensitivity to this drug or its components. Renally impaired patients (creatinine clearance < 30 ml/minute, and patients with decompensated hemolytic anemia and in children.

**DRUG INTERACTIONS**

Pentostatin (deoxycoformycin): use of fludarabine in combination with pentostatin is not recommended because of a very high incidence of fatal pulmonary toxicity. Adenosine uptake inhibitors: The therapeutic efficacy of fludarabine may be reduced by dipyridamole and other adenosine uptake inhibitors.

**ADVERSE EFFECTS**

Myelosuppression (neutropenia, thrombocytopenia and anemia), fever, chills, and infection. Edema, malaise, fatigue, anorexia, nausea, vomiting, and weakness.

**SPECIAL PRECAUTIONS**

When used in high doses, fludarabine is associated with blindness, coma and death. Use cautiously in pre-existing skin cancer.

## ► ANTIMETABOLITES &gt; OTHER AGENTS

**AZACITIDINE**

Other agent

**INDICATION**

Myelodysplastic syndromes.

**MECHANISM OF ACTION**

Causes hypomethylation of DNA, which leads to normalization of functional genes that controls cell-differentiation to promote normal cell maturation.

**DOSAGE**

Starting dose: Subcutaneous or IV infusion 75 mg/m<sup>2</sup> daily for 7 days

**CONTRAINDICATIONS**

Advanced malignant hepatic tumors, hypersensitivity to azacitidine or mannitol

**DRUG INTERACTIONS**

Not specified.

**ADVERSE EFFECTS**

Myelosuppression, renal tubular acidosis, renal dysfunction and injection site reactions.

**SPECIAL PRECAUTIONS**

Use with caution in patients with severe preexisting liver impairment, monitor patients with renal impairment for potential toxicity, assess liver profile and serum creatinine before starting the drug.

**DECITABINE**

Other agent

**INDICATION**

Myelodysplastic syndrome.

**MECHANISM OF ACTION**

Incorporated into the DNA and subsequently inhibits DNA methyltransferase, which is responsible for DNA hypomethylation

**DOSAGE**

Starting dose of 15 mg/m<sup>2</sup> continuous intravenous infusion for 3 days.

**CONTRAINDICATIONS**

Known hypersensitivity to decitabine.

**DRUG INTERACTIONS**

Not specified.

**ADVERSE EFFECTS**

Myelosuppression, constipation, edema, headache and nausea.

**SPECIAL PRECAUTIONS**

Complete blood count to be determined as the treatment is

associated with neutropenia and thrombocytopenia, consider early use of antibiotics due to risk of infections.

NEALARABINE		Other agent
<b>INDICATIONS</b> T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma when disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.	<b>DOSAGE</b> Adult dose: 1,500 mg/m <sup>2</sup> IV over a period of 2 hours on days 1, 3, and 5; repeat every 21 days. Children dose: 650 mg/m <sup>2</sup> IV over a period of 1 hour daily for successive 5 days; repeat every 21 days.	<b>ADVERSE EFFECTS</b> Anemia, thrombocytopenia, neutropenia, leucopenia, headache, peripheral neurologic disorders.
<b>MECHANISM OF ACTION</b> This prodrug accumulates in the form of active 5'-triphosphate in the leukemic blasts and causes inhibition of DNA synthesis and cell death.	<b>CONTRAINDICATIONS</b> Not specified.	<b>SPECIAL PRECAUTIONS</b> Monitor for presence of neurologic toxicity. Complete blood counts along with platelet count must be monitored during therapy.
	<b>DRUG INTERACTIONS</b> Not be administered with deaminase inhibitors such as pentostatin.	

► NATURAL PRODUCT CANCER CHEMOTHERAPY DRUGS > VINCA ALKALOIDS

VINBLASTINE		Vinca alkaloid
<b>INDICATIONS</b> Testicular cancer, Hodgkin's disease, other lymphomas, inoperable malignant neoplasms of the breast, bladder, and cervix, neuroblastoma, choriocarcinoma and Kaposi's sarcoma.	<b>DOSAGE</b> Adult: IV: <i>Histiocytic lymphoma; Hodgkin's disease; Kaposi's sarcoma; Lymphocytic lymphoma; Testicular cancer</i> : Initial 3.7 mg/m <sup>2</sup> ; increase dose weekly in increments based on hematological counts until leukocyte count decreases to about 3,000/mm <sup>3</sup> . Maximum dose of 18.5 mg/m <sup>2</sup> /week. Usual dose: 5.5-7.4 mg/m <sup>2</sup> /week.	<b>DRUG INTERACTIONS</b> Hepatotoxicity of paracetamol. Decreased anticonvulsant levels on concomitant use.
<b>MECHANISM OF ACTION</b> It is a mitotic inhibitor; binds to microtubular protein tubulin and causes disruption of mitotic spindle and interferes with cytoskeletal function, thus inhibiting metaphase.	<b>CONTRAINDICATIONS</b> Intrathecal administration, severe granulocytopenia, systemic infections and hypersensitivity.	<b>ADVERSE EFFECTS</b> Bone marrow depression, stomatitis, GI bleeding, leukopenia, alopecia, constipation, hypertension, malaise and bone pain.
		<b>SPECIAL PRECAUTIONS</b> Use cautiously in hepatic impairment. Avoid extravasation and contact with the eyes.

VINCRISTINE		Vinca alkaloid
<b>INDICATIONS</b> Acute leukemia, Hodgkin's lymphoma, Non-Hodgkin lymphomas, rhabdomyosarcoma, neuroblastoma and Wilm's tumor.	<b>CONTRAINDICATIONS</b> Hypersensitivity, Charcot-Marie-tooth syndrome.	<b>leucopenia/anemia, hypertension/hypotension, GI upsets, urinary retention.</b>
<b>MECHANISM OF ACTION</b> It is a rapidly acting alkylating agent useful for inducing remission in acute leukemias but not good for maintenance therapy.	<b>DRUG INTERACTIONS</b> Phenytoin: reduced blood phenytoin levels, increased seizure activity. Itraconazole: increased severity of neuromuscular side effects.	<b>SPECIAL PRECAUTIONS</b> IV use only (Intrathecal fatal). Avoid contamination of the eyes. Avoid extravasation or leakage. The dose to be adjusted to body weight in children and elderly. Alcohol may cause increased adverse effects. Use only if absolutely necessary and under expert medical supervision during lactation.
<b>DOSAGE</b> 1.4-1.5 mg/m <sup>2</sup> administered once weekly. Maximum dose: 2 mg/week.	<b>ADVERSE EFFECTS</b> Neuritic pain, paresthesias, motor difficulties, vestibular disturbances, inappropriate ADH secretion, severe bronchospasm, alopecia, rash,	

**Durogesic®**  
fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**  
Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**  
(Tramadol 37.5 mg + Paracetamol 325 mg)

**VINOSELBINE**

Vinca alkaloid

**INDICATIONS**

Non-small cell lung carcinoma, breast carcinoma, Hodgkin's disease, ovarian carcinoma, squamous cell carcinoma of the head and neck, cervical, SCLC, renal cell cancer and Kaposi's sarcoma.

**MECHANISM OF ACTION**

It is a semi-synthetic vinca alkaloid. It interferes with microtubules, which consists of mitotic spindle fibres leading to cell cycle arrest in the metaphase.

**DOSAGE**

Oral: Non-small cell lung cancer:

60 mg/m<sup>2</sup>/week for 3 week, up to 80 mg/m<sup>2</sup>/week depending on hematological counts. Intravenous *Non-small cell lung cancer*: As single agent: 30 mg/m<sup>2</sup>/week. Delay treatment if neutrophil count is <2000 cells/mm<sup>3</sup> until recovery. In combination therapy with cisplatin: 25-30 mg/m<sup>2</sup>/7 days. *Breast Cancer and Ovarian cancer*: 25 mg/m<sup>2</sup>/dose every 7 days. *Cervical cancer*: 30 mg/m<sup>2</sup>/dose on days 1 and 8 of a 21-day treatment cycle.

**CONTRAINDICATIONS**

Hypersensitivity, intrathecal administration as it is extremely irritating.

**ADVERSE EFFECTS**

Granulocytopenia, anemia, thrombocytopenia, nausea, vomiting, constipation, peripheral neuropathy, dyspnea, cough, bronchospasm, alopecia, injection, site reaction, myalgia, muscle weakness and jaw pain.

**SPECIAL PRECAUTIONS**

Use cautiously in patients with compromised bone marrow reserve, hepatic insufficiency, neuropathy.

► NATURAL PRODUCT CANCER CHEMOTHERAPY DRUGS > TAXANE AND RELATED DRUGS

**DOCETAXEL**

Taxane and related drug

**INDICATIONS**

Breast cancer, non-small cell lung cancer, cancer of bladder, esophagus, stomach, head, neck, ovaries and prostate.

**MECHANISM OF ACTION**

It binds to beta-tubulin subunit of microtubule and antagonises the disassembly of this cytoskeleton protein causing arrest in mitosis.

**DOSAGE**

Individualized as per manufacturer's recommendations. Adult: IV

therapy: *Breast cancer*: Starting: 60-100 mg/m<sup>2</sup> once 3 weekly as a single agent.

**CONTRAINDICATIONS**

Previous severe hypersensitivity reaction to docetaxel, the solvent or polysorbate 80, severe neutropenia, pregnancy, severe liver impairment.

**DRUG INTERACTIONS**

Cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin.

**ADVERSE EFFECTS**

Erythematous patches, eruptions, scleroedema, onycholysis, alopecia, nausea, vomiting, diarrhea, stomatitis, increases in hepatic transaminases, bilirubin, and alkaline phosphatase, mucositis, asthenia, arthralgia, myalgia, paroxysmal atrial tachycardia, atrial flutter, dysrhythmia, hypertension and heart failure.

**SPECIAL PRECAUTIONS**

Use cautiously in lactation and hepatic impairment.

**PACLITAXEL**

Taxane and related drug

**INDICATIONS**

Indicated after the failure of the first-line treatment: neoplasms of the breast and ovary, tumors of the lung and prostate, malignant melanoma and Kaposi's sarcoma.

**MECHANISM OF ACTION**

It binds to beta tubulin subunit of microtubule and antagonises the disassembly of this cytoskeleton protein, causing arrest in mitosis.

**DOSAGE**

Adults: 135-175 mg/m<sup>2</sup> by IV infusion over 3 hours. The dose

repeated after 3 or more weeks depending on tolerance.

**CONTRAINDICATIONS**

Severe hepatic impairment, hypersensitivity.

**DRUG INTERACTIONS**

Use with cisplatin causes myelosuppression.

**ADVERSE EFFECTS**

Alopecia, myalgia, arthralgia, GI disturbances, mucositis, bradycardia, conduction abnormalities, chest pain, flushing and rashes.

**SPECIAL PRECAUTIONS**

Avoid extravasation. Use cautiously in hepatic dysfunction. Monitor blood counts regularly. The dose is not repeated with neutrophils < 1500/mm<sup>3</sup> and platelets <100,000/mm<sup>3</sup>. Safety not established in children. May adversely affect nursing infant.

► NATURAL PRODUCT CANCER CHEMOTHERAPY DRUGS > EPIPODOPHYLLOTOXINS

ETOPOSIDE	 !  	Epidopophyllotoxin
<b>INDICATIONS</b> Testicular tumors, small cell lung cancer, acute monocytic leukemia, acute myelomonocytic leukemia and Hodgkin's disease.	intervals of 3-4 weeks. <i>Small cell lung cancer:</i> IV: 35 mg/m <sup>2</sup> /day for 4 day to 50 mg/m <sup>2</sup> /day for 5 days. Repeated after 3-4 weeks.	diarrhea, hypotension, fever/chills, bronchospasm and allergic reaction.
<b>MECHANISM OF ACTION</b> It inhibits DNA synthesis causing arrest of cell cycle. It also inhibits cells from entering cell cycle.	<b>CONTRAINDICATION</b> Hypersensitivity.	<b>SPECIAL PRECAUTIONS</b> Use with caution in infections. Monitor hepatic, renal and hematological functions. Avoid contact with the skin, mucosa and eye. Avoid extravasation. Safety and effectiveness not established in children. It causes fetal harm if used in pregnancy.
<b>DOSAGE</b> Adults: <i>Testicular carcinoma:</i> 50 - 100 mg/m <sup>2</sup> /day - IV for 5 days. (slow IV over 30 - 60 mins) repeated after	<b>DRUG INTERACTIONS</b> Cisplatin causes ↓ in etoposide clearance and increased toxicity.	<b>ADVERSE EFFECTS</b> Myelosuppression, reversible alopecia, pigmentation, optic neuritis, anorexia, nausea/vomiting,

► NATURAL PRODUCT CANCER CHEMOTHERAPY DRUGS > CAMPTOTHECINS

IRINOTECAN	 !  	Camptothecin
<b>INDICATION</b> Metastatic carcinoma of the colon or rectum.	dose is 125 mg/m <sup>2</sup> , patients should be carefully monitored for toxicity.	<b>ADVERSE EFFECTS</b> Abdominal discomfort, vomiting, diarrhea, nausea, leucopenia, neutropenia, anemia, hemorrhage body pain, asthenia, insomnia, dizziness.
<b>MECHANISM OF ACTION</b> Irinotecan inhibits topoisomerase I, an enzyme involved in DNA replication.	<b>CONTRAINDICATIONS</b> Known hypersensitivity to irinotecan.	<b>SPECIAL PRECAUTIONS</b> Because of its possibility of causing dehydration in diarrhea, caution should be observed in the use of irinotecan with diuretics.
<b>DOSAGE</b> Varies in weekly and once every three week schedule. All dosages are to be administered as IV infusion over 90 minutes. Weekly dose schedule: The usual starting	<b>DRUG INTERACTION</b> Other antineoplastic agents: Side-effects like diarrhea and myelosuppression may be exacerbated. Dexamethasone: lymphocytopenia has been observed when coadministered.	

TOPOTECAN	 !  	Camptothecin
<b>INDICATIONS</b> Metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy. Small cell lung cancer disease after failure of first line chemotherapy. Cervical cancer.	5 consecutive days, starting on day 1 of a 21 day course. In absence of tumor progression, a minimum of four courses are recommended, as tumor response may be delayed.	i.e., 24 hours after completion of treatment with topotecan.
<b>MECHANISM OF ACTION</b> Topotecan inhibits topoisomerase I, an enzyme involved in DNA replication.	<b>CONTRAINDICATIONS</b> Known hypersensitivity to topotecan, patients with severe bone marrow depression.	<b>ADVERSE EFFECTS</b> Abdominal discomfort, intestinal obstruction, vomiting, diarrhea, nausea, stomatitis, anorexia. Bone marrow suppression (primarily neutropenia, thrombocytopenia, anemia).
<b>DOSAGE</b> Before administration of topotecan, patient should have a baseline neutrophil count of > 1500 cells/mm <sup>3</sup> and a platelet count of > 100000 cell/mm <sup>3</sup> . The recommended starting dose is 1.5 mg/m <sup>2</sup> by IV infusion over 30 minutes daily for	<b>DRUG INTERACTIONS</b> Other antineoplastic agent: Myelosuppression may be more severe if topotecan is given with cisplatin. G-CSF: Coadministration of G-CSF and topotecan may prolong duration of neutropenia. If G-CSF has to be used, it should be started only on day 6 of the course	<b>SPECIAL PRECAUTIONS</b> Use with caution in pregnant women as it may cause fetal harm. Contraindicated in lactating mothers as drug is secreted in breast milk. Use cautiously in children as their safety and efficacy have not been established.

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## ► NATURAL PRODUCT CANCER CHEMOTHERAPY DRUGS &gt; OTHER AGENTS

ESTRAMUSTINE		Other agent
<p><b>INDICATIONS</b> Metastatic and/or progressive carcinoma of the prostate.</p> <p><b>MECHANISM OF ACTION</b> Estramustine phosphate is a molecule formed by combining estradiol and nornitrogen mustard by a carbamate link. Estramustine exerts their cytotoxic effects principally by binding to tubulin and/or microtubule-associated proteins. Binding of estramustine to these protein subunits induces depolymerization of microtubules, resulting in cellular metaphase arrest. The drug may damage the cell membrane, promote DNA breakage, interfere with DNA replication, and induce cellular apoptosis in other cell lines (e.g., glioma cells and colon cancer cells).</p>	<p><b>DOSAGE</b> Adult: PO: 560-840 mg/day in divided doses, may adjust to 0.14-1.4 g/day according to response and GI tolerance. Treat for at least 30-90 days before assessing treatment benefits.</p> <p><b>CONTRAINdications</b> Known hypersensitivity to either estradiol or to nitrogen mustard, active thrombophlebitis or thromboembolic disorders.</p> <p><b>DRUG INTERACTIONS</b> Decreased absorption when estramustine is used concomitantly with calcium-containing foods or beverages (e.g., milk, milk products) or drugs (e.g., calcium-containing antacids).</p>	<p><b>ADVERSE EFFECTS</b> Cardiac arrest, cerebrovascular accident, myocardial infarction, thrombophlebitis, pulmonary emboli, congestive heart failure, edema, dyspnea, nausea, diarrhea, anorexia, flatulence, vomiting, gastrointestinal bleeding, headache and anxiety.</p> <p><b>SPECIAL PRECAUTIONS</b> Use with caution in patients with cerebrovascular or coronary artery diseases, patients with diabetes mellitus should be carefully monitored during estramustine therapy.</p>

## ► ANTITUMOR ANTIBIOTICS &gt; ANTHRACYCLINES

DOXORUBICIN		Anthracycline
<p><b>INDICATIONS</b> Leukemias, sarcomas, lymphomas, neuroblastoma, Wilms' tumor, malignant neoplasms (bladder, breast, lung, ovary, stomach and thyroid), other tumors: cervix, endometrium, liver, pancreas and thyroid, gestational trophoblastic tumors, retinoblastomas, myeloma and Kaposi's sarcoma.</p> <p><b>MECHANISM OF ACTION</b> It causes break in DNA strands by activating topoisomerase II and generating quinone type free radicals. It is effective in acute leukemias and many solid tumors.</p> <p><b>DOSAGE</b> Adult: IV: AIDS-related Kaposi's</p>	<p><i>sarcoma:</i> As pegylated liposome: 20 mg/m<sup>2</sup> once 2-3 weekly. <i>Ovarian carcinoma:</i> As pegylated liposome: 50 mg/m<sup>2</sup> once 4 weekly. <i>Metastatic breast carcinoma w/ cyclophosphamide:</i> 60-75 mg/m<sup>2</sup> once 3 weekly. <i>Irrigation Local malignant neoplasms in the bladder:</i> As 1 mg/mL soln: Instill 50 mL into the bladder for 1 hr once monthly.</p> <p><b>CONTRAINDICATIONS</b> Severe marrow depression, Hypersensitivity.</p> <p><b>DRUG INTERACTIONS</b> Doxorubicin interacts with a number of other drugs e.g. antibiotics (aminoglycosides), steroids, amio-phylline and propranolol.</p>	<p><b>ADVERSE EFFECTS</b> Nausea/vomiting, loss of appetite, hair loss, diarrhea, mouth ulcers and palpitations.</p> <p><b>SPECIAL PRECAUTIONS</b> Use cautiously in cardiac disease and hepatic impairment. It should not be given IM/SC. Avoid extravasation. It enhances the adverse effects of irradiation. Reduced dose necessary in elderly and children. Doxorubicin may cause birth defects or premature birth. The drug passes into breastmilk and may affect the infant adversely.</p>



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**DAUNORUBICIN**

Anthracycline

**INDICATION**

Acute leukemia

**MECHANISM OF ACTION**

It forms a complex with DNA and interferes with synthesis of nucleic acids, with most marked effect on cells in S-phase. It also has immunosuppressant action.

**DOSAGE**

Adult: IV: Acute leukemia: 30-45 mg/m<sup>2</sup>/day on days 1-3 of the induction regimen and days 1 and 2 of subsequent courses. May repeat course 3-6 week later. Children: For acute lymphoblastic leukemia: 25 mg/m<sup>2</sup> body surface area (BSA) once weekly in combination with other regimens.

**CONTRAINDICATIONS**

Heart failure, hypersensitivity, bone marrow suppression.

**DRUG INTERACTIONS**

Immunization with live vaccines not recommended as daunorubicin is immunosupresant. Concurrent radiation leads to enhanced radiation reaction. Incompatible with heparin, aluminium and dexamethasone.

**ADVERSE EFFECTS**

Bone marrow suppression, cardiac toxicity, cardiomyopathy, GI disturbances, stomatitis, alopecia and dermatological reactions. Extravasation of daunorubicin may cause severe local tissue necrosis

damaging surrounding muscles, tendons and nerves.

**SPECIAL PRECAUTIONS**

Monitor blood counts and perform ECG test regularly. Use with caution in pregnancy, lactation, elderly, liver dysfunction. Children appear to be at risk for delayed cardiac toxicity and cardiomyopathy leading to CHF during early adulthood. So cautious use is advocated. Safety in pregnancy not established. Due to potential for serious adverse reactions in nursing infants from daunorubicin, mothers should be advised to discontinue nursing during therapy. Avoid alcohol during therapy.

**EPIRUBICIN**

Anthracycline

**INDICATIONS**

Breast carcinoma, malignant lymphomas, soft tissue sarcoma, gastric, hepatic, pancreatic and sigma-rectum carcinomas, head and neck carcinoma, lung carcinoma, ovarian carcinoma and leukemias.

**MECHANISM OF ACTION**

The mechanism of action is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localization in the nucleus and inhibition of nucleic acid synthesis and mitosis.

**DOSAGE**

Adult: IV: Acute leukemias; Lymphoma; Multiple myeloma: As a single agent: 60-90 mg/m<sup>2</sup> 3-4 weekly. Maximum (total cumulative

dose): 0.9-1 g/m<sup>2</sup>. Palliative care: 12.5-25 mg/m<sup>2</sup> once weekly. Adjuvant treatment in axillary-node positive breast cancer. Recommended starting doses: 100-120 mg/m<sup>2</sup> as a single dose on day 1 or as 2 divided doses on days 1 and 8 of each 28-day cycle. Repeat for 6 cycles. For palliative care: 12.5-25 mg/m<sup>2</sup> once weekly. IV Solid tumors: Adult: As a single agent: 60-90 mg/m<sup>2</sup> every 3-4 week. May divide dose over 2-3 days if desired.

**CONTRAINDICATIONS**

In patients with marked myelosuppression induced by previous treatments with other antitumor agents or by radiotherapy. Previous history of cardiac impairment and hypersensitivity.

**DRUG INTERACTIONS**

Paclitaxel and other anthracyclines. Cimetidine, heparin, antineoplastic drugs, cardiotoxic drugs and alcohol.

**ADVERSE EFFECTS**

Alopecia, mucositis, stomatitis with areas of painful erosions, gastrointestinal disturbances, such as nausea, vomiting, diarrhea and hyperpyrexia.

**SPECIAL PRECAUTIONS**

Use cautiously in pregnancy. White and red blood cells and platelet counts should be carefully monitored. Cardiac function must be carefully monitored.

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**IDARUBICIN**

Anthracycline

**INDICATION**

Acute non-lymphoblastic leukemia (ANLL), acute myeloid leukemia (AML).

**MECHANISM OF ACTION**

Idarubicin inhibits the synthesis of nucleic acids (DNA and RNA) and interacts with the enzyme topoisomerase II by intercalating between DNA base pairs. The lipophilic nature of the drug makes it more available for cellular uptake as compared to other anthracyclines. In addition, anthracyclines bind and forms drug-iron complex which undergoes reduction to generate free radicals leading to cell death. Idarubicin is cell cycle phase-specific and arrests growth in the G1 and G2 phase.

**DOSAGE**

Adult: Oral: *Acute myeloid leukemia:* 30 mg/m<sup>2</sup> daily for 3 days as single

agent or 15-30 mg/m<sup>2</sup> daily for 3 days in combination with other drugs. *Intravenous Acute myeloid leukemia:* Adult: Induction: 12 mg/m<sup>2</sup> daily for 3 days, in combination with cytarabine. Dose to be given as slow inj (over 10-15 minutes).

**CONTRAINDICATIONS**

Hypersensitivity, contraindicated in severe myelosuppression, uncontrolled infection, pregnancy and lactation.

**DRUG INTERACTION**

Coadministration with live vaccines leads to possible infection and may impair immune response to vaccines

**ADVERSE EFFECTS**

Infection, nausea, vomiting, hair loss, abdominal cramps, diarrhea, mental illness, fever, headache, nerve disease, lung allergy and

seizures, Severe myelosuppression, leucopenia, thrombocytopenia, cardiotoxicity, hyperuricemia, local tissue necrosis upon extravasation, increased bilirubin and transaminases, headache, peripheral neuropathy, mental status changes.

**SPECIAL PRECAUTIONS**

Use cautiously in patients with systemic infections, previous anthracyclines therapy, preexisting cardiac disease, renal and hepatic impairment. One should monitor cardiac function, CBC, bilirubin levels and withhold if bilirubin is >20 mcg/ml.

**MITOXANTRONE**

Anthracycline

**INDICATIONS**

Acute myeloid leukemia, breast cancer, liver cancer, lymphoma, prostate cancer, multiple sclerosis.

**MECHANISM OF ACTION**

It is a doxorubicin analogue with similar mechanism of action but less cardiotoxicity.

**DOSAGE**

Adult: IV: *Acute myeloid leukemia:* 12 mg/m<sup>2</sup>/day for 5 days to induce remission. *Breast cancer; liver cancer; lymphoma:* Initial dose: 14mg/m<sup>2</sup>. Adjust subsequent doses based on degree of myelosuppression. As part of a combination regimen: May reduce initial dose to 10-12

mg/m<sup>2</sup>. *Multiple sclerosis:* Initial: 12 mg/m<sup>2</sup> once every 3 mth provided neutrophil count is >1,500 cells/mm<sup>3</sup> and LVEF >50%.

**CONTRAINDICATION**

Hypersensitivity, myelosuppression, cardiac defects, abnormal liver function.

**DRUG INTERACTION**

Cyclosporine causes ↑ cyclosporine CNS adverse effects. Other cardiotoxic agents ↑ cardiotoxicity.

**ADVERSE EFFECTS**

Nausea/vomiting, loss of appetite, hair loss, diarrhea, mouth ulcers, palpitations.

**SPECIAL PRECAUTIONS**

Use cautiously in cardiac disease, hepatic impairment. It should not be given IM/SC. Avoid extravasation. It enhances the adverse effects of irradiation. Increased risk of side effects in elderly.

► ANTITUMOR ANTIBIOTICS > OTHER ANTIBIOTICS

BLEOMYCIN		Other antibiotic
<b>INDICATIONS</b> Palliative or adjuvant treatment in: squamous cell carcinoma of the head, neck, penis, cervix and vulva; Hodgkin and Non-Hodgkin lymphomas, testicular carcinoma and malignant effusion.	week or 30,000 IU twice weekly, in 3-4 weekly intervals up to a total cumulative dose of 500,000 IU. IM: Lymphoma: 15,000 IU once or twice a week, up to a total cumulative dose of 225,000 IU.	fever and chills, nausea/vomiting, skin rashes, alopecia, stomatitis, hypertension and vascular complications.
<b>MECHANISM OF ACTION</b> It chelates copper or iron, produces superoxide ions and interpolates between DNA strands causing chain scission and inhibition of repair.	<b>CONTRAINDICATION</b> Hypersensitivity.	<b>SPECIAL PRECAUTIONS</b> Close monitoring during and after the treatment. Use cautiously in renal, hepatic and pulmonary impairment. Reduced dose may be necessary in elderly. Alcohol may cause increased adverse effects.
<b>DOSAGE</b> Adult: IV/IM: Squamous cell or testicular tumors: 15,000 IU 3 times/	<b>DRUG INTERACTIONS</b> Cisplatin causes ↑ pulmonary toxicity. Nephrotoxic agents cause ↑ nephrotoxicity.	<b>ADVERSE EFFECTS</b> Pulmonary fibrosis, idiosyncratic reactions, renal and hepatic toxicity,

MITOMYCIN		Other antibiotic
<b>INDICATIONS</b> Disseminated adenocarcinoma, lymphosarcoma and seminoma, others-melanoma, leukemias and solid tumors.	combination and on bone marrow recovery.	toxicity, congestive heart failure, stomatitis, alopecia, pulmonary infiltrates, hemolytic anemia, pulmonary edema and GI upsets.
<b>MECHANISM OF ACTION</b> It is a toxic antibiotic with antitumor activity, isolated from streptomyces.	<b>CONTRAINDICATIONS</b> Hypersensitivity, thrombocytopenia, bleeding disorders, coagulation disorders, not to be given IM or SC.	<b>SPECIAL PRECAUTIONS</b> Close monitoring during and after the treatment. The treatment is stopped if platelet count falls below 1,00,000/mm <sup>3</sup> or WBC below 4,000/mm <sup>3</sup> . Dose reduction necessary in children and elderly. Monitor renal function.
<b>DOSAGE</b> Adult: IV: Solid tumors: 4-10 mg (0.06-0.15 mg/kg) given at 1-6 weekly intervals depending on whether other drugs are given in	<b>DRUG INTERACTIONS</b> Doxorubicin causes mitomycin cardiotoxicity. Vinca alkaloids cause acute bronchospasm.	<b>ADVERSE EFFECTS</b> Bone marrow suppression, renal

► MISCELLANEOUS DRUGS > TYROSINE-KINASE INHIBITORS

DASATINIB		Tyrosine-kinase inhibitor
<b>INDICATIONS</b> Chronic myeloid leukemia (CML) in chronic phase and Philadelphia-chromosome positive acute lymphoblastic leukemia (ALL).	ALL: Initial: 140 mg once daily, up to 180 once daily.	<b>SPECIAL PRECAUTIONS</b> Monitor complete blood counts regularly as myelosuppression may occur. Bleeding related events associated with severe thrombocytopenia. Fluid retention including ascites, edema, pleural effusion. Monitor patients with QT prolongation, congestive heart failure, left ventricular dysfunction and myocardial infarction.
<b>MECHANISM OF ACTION</b> It is a tyrosine kinase inhibitor and inhibits SRC kinase. Tyrosine kinases mediate cellular differentiation, proliferation and survival.	<b>CONTRAINDICATION</b> Not specified.	<b>DRUG INTERACTIONS</b> Dasatinib drug levels may increase with concomitant use of CYP3A4 inhibitors. Dasatinib drug levels may decrease with CYP3A4 inducers, antacids, H <sub>2</sub> antagonists and proton pump inhibitors.
<b>DOSAGE</b> Adult: PO: Chronic phase CML: Initial: 100 mg once daily, up to 140 mg once daily. Accelerated, myeloid or lymphoid blast phase CML or Philadelphia chromosome-positive	<b>ADVERSE EFFECTS</b> Myelosuppression, nausea, vomiting, headache, fluid retention, hypocalcemia and pleural effusion.	

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**ERLOTINIB**

Tyrosine-kinase inhibitor

**INDICATIONS**

Maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) where disease has not progressed after four cycles of platinum-based first-line chemotherapy, or after failure of at least one prior chemotherapy regimen. In combination with gemcitabine, for the first-line treatment of locally advanced, unresectable or metastatic pancreatic cancer.

**MECHANISM OF ACTION**

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR).

**DOSAGE**

*NSCLC:* 150 mg/day; *Pancreatic cancer:* 100 mg/day in combination with gemcitabine.

**ADVERSE EFFECTS**

Rash, diarrhea, anorexia, stomatitis, pruritus, infection, infrequent serious interstitial lung disease (ILD).

**SPECIAL PRECAUTIONS**

In patients with renal and hepatic impairment.

**IMATINIB**

Tyrosine-kinase inhibitor

**INDICATIONS**

Chronic myeloid leukemia (CML), unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

**MECHANISM OF ACTION**

It is a protein-tyrosine kinase inhibitor that inhibits Bcr-Abl tyrosine kinase. It is also an inhibitor of the receptor tyrosine kinases for platelet derived growth factor and stem cell factor C-kit and inhibits their mediated cellular events.

**DOSAGE**

To be administered orally with a meal and a large glass of water. Range of dosage to be adjusted according to therapeutic response

and adverse effects. *Chronic Phase CML:* 400-600 mg/day. Accelerated Phase or blast crisis CML: 600 mg/day. *Unresectable and/or metastatic malignant GIST:* 400 mg/day.

**CONTRAINDICATION**

Hypersensitivity.

**DRUG INTERACTIONS**

Ketoconazole, itraconazole, erythromycin, and clarithromycin may increase plasma concentration of imatinib, while dexamethasone, phenytoin, carbamazepine, rifampicin, may decrease the plasma concentration of imatinib. It will increase plasma concentration of triazolo-benzodiazepines, dihydropyridine, calcium channel

blockers, certain HMG-CoA reductase inhibitors and warfarin.

**ADVERSE EFFECTS**

Nausea, vomiting, diarrhea, abdominal pain, rash, edema, and muscle cramps. Local or generalized fluid retention and rapid weight gain, cytopenias and hepatotoxicity.

**SPECIAL PRECAUTIONS**

Dose adjustment/reduction or treatment interruption is recommended if a severe adverse effect develops.

**NILOTINIB**

Tyrosine-kinase inhibitor

**INDICATION**

Philadelphia chromosome positive chronic myelogenous leukemia.

**MECHANISM OF ACTION**

Blocks the breakpoint cluster region tyrosine kinase.

**DOSAGE**

Newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia-CP: 300-400 mg orally twice daily. Resistant or intolerant Philadelphia chromosome positive chronic myelogenous leukemia-CP: 400 mg orally twice daily.

**CONTRAINDICATIONS**

Not to be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

**DRUG INTERACTIONS**

May alter serum concentration of other drugs. Drug concentrations may be affected by CYP3A4 inhibitors. CYP3A4 inducers may alter serum concentration of this drug.

**ADVERSE EFFECTS**

QT prolongation, bone marrow suppression, elevation in lipase levels and hepatotoxicity, nausea,

vomiting, rash, pruritus, headache, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, and asthenia.

**SPECIAL PRECAUTIONS**

May cause myelosuppression, sudden death, raises serum lipase, liver function deviation, and electrolyte imbalance.

SORAFENIB		Tyrosine-kinase inhibitor
<p><b>INDICATIONS</b> Renal cell carcinoma, unresectable hepatocellular carcinoma and differentiated thyroid carcinoma</p> <p><b>MECHANISM OF ACTION</b> It is a multikinase inhibitor and inhibits intracellular and extracellular kinases thus decreasing renal cell proliferation</p> <p><b>DOSAGE</b> 400 mg oral dosage twice daily without food.</p>	<p><b>CONTRAINDICATION</b> Hypersensitivity.</p> <p><b>DRUG INTERACTIONS</b> Avoid use with strong CYP3A4 inducers.</p> <p><b>ADVERSE EFFECTS</b> Rash, hand-foot skin reaction, diarrhea, pruritus and increases serum lipase.</p>	<p><b>SPECIAL PRECAUTIONS</b> Use with caution in patients with cardiac ischemia or infarction. Discontinue use in patients with bleeding. Monitor blood pressure with therapy. Dermatological reactions are common-interrupt or decrease dosing. Discontinue in patients with gastrointestinal perforations. Monitor TSH levels</p>

SUNITINIB		Tyrosine-kinase inhibitor
<p><b>INDICATIONS</b> Gastrointestinal stromal tumor after disease progression or intolerance to imatinib and advanced renal cell cancer.</p> <p><b>MECHANISM OF ACTION</b> Inhibits multiple tyrosine kinases that subsequently inhibit platelet-derived growth factor, stem-cell factor receptor, fms-like receptor, growth factor, colony-stimulating growth factor receptor type 1 and glial cell line derived neurotrophic factor receptor.</p> <p><b>DOSAGE</b> Oral dose 50 mg once-daily, administered with or without food,</p>	<p>4 weeks on treatment followed by 2 weeks off treatment</p> <p><b>CONTRAINDICATIONS</b> Not specified.</p> <p><b>DRUG INTERACTIONS</b> Dose to be reduced with CYP3A4 inhibitors, dose to be increased with CYP3A4 inducers.</p> <p><b>ADVERSE EFFECTS</b> Fever, fatigue, asthenia, diarrhea, nausea, mucositis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, back pain,</p>	<p>arthralgia, extremity pain, altered taste, headache, cough, dyspnea, anorexia, and bleeding.</p> <p><b>SPECIAL PRECAUTIONS</b> Hepatotoxicity has been reported; monitor liver function throughout treatment. It should be interrupted in cases of grade 3 or 4 drug-related hepatic events. Cardiac toxicity reported, monitor patient for sign and symptoms of congestive heart failure. Prolonged QT intervals and Torsade de Pointes. Hypertension may occur. Thyroid dysfunction may occur. Reports of hemorrhagic events.</p>

## ► MISCELLANEOUS DRUGS > MONOCLONAL ANTIBODIES

BEVACIZUMAB		Monoclonal antibodies
<p><b>INDICATIONS</b> Metastatic colorectal cancer in combination with intravenous 5-fluorouracil-based chemotherapy. Metastatic colorectal cancer in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy. Metastatic non-squamous non-small cell lung cancer and renal cell cancer.</p> <p><b>MECHANISM OF ACTION</b> Binds and prevents VEGF-A from interacting with target VEGF-A receptors. Inhibits tumor vascular</p>	<p>permeability and enhances blood flow and drug delivery.</p> <p><b>DOSAGE</b> <i>Metastatic colorectal cancer:</i> Intravenous 5 mg/kg every 2 weeks with bolus-irinotecan, leucovorin (folinic acid), and fluorouracil, intravenous 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy.</p> <p><b>CONTRAINDICATION</b> Not specified.</p>	<p><b>ADVERSE EFFECTS</b> Hypertension, increased incidence of arterial thromboembolic events, wound healing complications, gastrointestinal perforations and proteinuria.</p> <p><b>SPECIAL PRECAUTIONS</b> Chances of perforation or fistula, venous thromboembolic events, discontinue in events of hypertensive crisis or hypertensive encephalopathy, discontinue in posterior reversible encephalopathy syndrome. Ovarian failure reported in females.</p>



<b>CETUXIMAB</b>				Monoclonal antibodies
	<b>INDICATIONS</b> Metastatic colon cancer, locally advanced head and neck cancer and non-small cell lung cancer.	<b>DOSAGE</b> Initial dose: Administer 400 mg/m <sup>2</sup> as a 120-minute intravenous infusion followed by 250 mg/m <sup>2</sup> weekly infused over 60 minutes.	<b>ADVERSE EFFECTS</b> Infusion reactions, skin rash, hypomagnesemia, fatigue and interstitial lung disease.	
<b>MECHANISM OF ACTION</b> Acts against epidermal growth factor receptors, enhances response to chemotherapy and radiotherapy.	<b>CONTRAINDICATION</b> Not specified.	<b>DRUG INTERACTIONS</b> Not specified.	<b>SPECIAL PRECAUTIONS</b> Infusion reactions and cardiopulmonary arrest. Pulmonary symptoms have been reported. Monitor electrolyte levels due to reports of hypomagnesemia.	
<b>PANITUMUMAB</b>				Monoclonal antibodies
	<b>INDICATIONS</b> Metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy.	<b>DOSAGE</b> Intravenous dose: 6 mg/kg every 14 days as an infusion over 60 minutes ( $\leq$ 1000 mg) or 90 minutes ( $>$ 1000 mg).	<b>ADVERSE EFFECTS</b> Erythema, dermatitis acneiform, pruritus, exfoliation, rash,	
<b>MECHANISM OF ACTION</b> Binds to EGFR and inhibits downstream EGFR signaling, enhances response to chemotherapy and radiotherapy.	<b>CONTRAINDICATION</b> Not specified.		<b>SPECIAL PRECAUTIONS</b> Discontinue therapy in events of dermatological toxicities or infusion reaction. Increased toxicity with combination chemotherapy. Monitor for electrolyte imbalance.	
<b>RITUXIMAB</b>				Monoclonal antibodies
	<b>INDICATIONS</b> Non-Hodgkin's lymphoma and relapsed follicular lymphoma.	<b>DOSAGE</b> min, if tolerated. Rate should not be exceeding by 400 mg/hr.  In B-cell lymphoma, rituximab should be used with CVP (cyclophosphamide, vincristine, and prednisolone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen: 375 mg/m <sup>2</sup> BSA given on day 1 of each 21-day cycle, for 8 doses. In case not progressed, 375 mg/m <sup>2</sup> BSA may be given once in a week, for 4 doses, may repeat every 6 months, for up to 16 doses. Maintenance dose: 375 mg/m <sup>2</sup> BSA is given once every 3 months until disease progression or a max period of 2 years.	<b>ADVERSE EFFECTS</b> Severe adverse effects comprises of pulmonary or cardiac toxicity during infusion, severe mucocutaneous reactions, severe cytokine release syndrome associated with tumor lysis syndrome and toxic epidermal necrolysis.	
<b>MECHANISM OF ACTION</b> Rituximab is a chimeric monoclonal antibody that binds on the cell surface of CD20 antigen and human Fc receptors. This binding of antigen and antibody is responsible for cell-killing in lymphomas and arthritis.	<b>CONTRAINDICATIONS</b> Lactation. Hypersensitivity.	<b>DRUG INTERACTION</b> Cisplatin, vaccines (risk of infections in patients immunized with live vaccines), clozapine (low WBC counts).	<b>SPECIAL PRECAUTIONS</b> Fever and rigors. Pruritus, skin rashes, dyspnea, bronchospasm, angioedema, transient hypotension, flushing, tumor lysis syndrome, respiratory failure, thrombocytopenia, neutropenia and anemia. Hypersensitivity reactions.	
	<b>DOSAGE</b> <i>Adult: Non-Hodgkin's lymphoma and Refractory or relapsed follicular lymphoma:</i> As a single agent, 375 mg/m <sup>2</sup> BSA by IV infusion once in a week, for 4 doses. The initial rate is 50 mg/hr and may increase slowly every 30 min. May further increase upto 100 mg/hr every 30 min. Rate should not be exceeding by 400 mg/hr.  The subsequent infusions can be started at 100 mg/hr and increased by 100 mg/hr every 30			

► MISCELLANEOUS DRUGS > GROWTH FACTOR RECEPTOR INHIBITOR

GEFITINIB						Growth factor receptor inhibitor
<b>INDICATIONS</b>						
Locally advanced or metastatic non-small cell lung cancer.						
<b>MECHANISM OF ACTION</b>						
Gefitinib, a synthetic anilino-quinazoline, inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including epidermal growth factor receptor (EGFR) tyrosine kinase.						
<b>DOSAGE</b>						
Oral: 250 mg once-daily.						

► MISCELLANEOUS DRUGS > RETINOIC ACID DERIVATIVE

TRETINOIN						Retinoic acid derivative
<b>INDICATION</b>						
Acute promyelocytic leukemia following progression or relapse with anthracycline therapy.						
<b>MECHANISM OF ACTION</b>						
Promotes maturation of early promyelocytic cells and is specific to the t(15;17) cytogenic marker. It is not cytotoxic.						
<b>DOSAGE</b>						
PO 45 mg/m <sup>2</sup> /day in 2 divided doses.						
<b>CONTRAINDICATIONS</b>						
Hypersensitivity to tretinoin.						
<b>DRUG INTERACTIONS</b>						
Increases risk of fatal thrombotic complications with anti-fibrinolytic agents.						
<b>ADVERSE EFFECTS</b>						
Vitamin A toxicity: manifesting as headache, fever, dry skin and mucous membrane, pruritus, skin rash and conjunctivitis. Retinoic acid syndrome: fever, hypotension, respiratory distress, leukocytosis and weight gain.						
<b>SPECIAL PRECAUTIONS</b>						
Chest radiography may confuse diagnosis of pneumonia in neutropenic patients, causes transient elevation in liver enzymes: Discontinue temporarily if LFT exceed 5 times upper limit of normal. Increases cholesterol and triglyceride levels. Reduce dose if intractable headache occurs.						

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(Tramadol 37.5 mg + Paracetamol 325 mg)

## ► MISCELLANEOUS DRUGS &gt; CORTICOSTEROIDS

DEXAMETHASONE		Corticosteroid
<p><b>INDICATIONS</b> Prophylaxis of nausea and vomiting associated with cytotoxic therapy, cerebral edema caused by malignancy.</p> <p><b>MECHANISM OF ACTION</b> It is a long acting anti-inflammatory and immunosuppressive drug.</p> <p><b>DOSAGE</b> <i>Cerebral edema caused by malignancy:</i> Adult: As phosphate: 10 mg IV followed by 4 mg IM every 6 hr until response is achieved, usually after 12-24 hr. May reduce dosage after 2-4 days then gradually discontinued over 5-7 days.</p>	<p><i>Prophylaxis of nausea and vomiting associated with cytotoxic therapy:</i> Adult: 10-20 mg 15-30 minutes before administration of chemotherapy on each treatment day. For continuous infusion regimen: 10 mg every 12 hr on each treatment day.</p> <p><b>CONTRAINdications</b> Renal impairment, diabetes mellitus, psychosis, tuberculosis, CCF, systemic infection.</p> <p><b>DRUG INTERACTIONS</b> Not specified.</p>	<p><b>ADVERSE EFFECTS</b> Indigestion, weight gain, acne and other skin effects, fluid retention, muscle weakness, mood changes.</p> <p><b>SPECIAL PRECAUTIONS</b> Use cautiously in peptic ulcer, glaucoma, tuberculosis, depression or mental illness, herpes infection, liver dysfunction. May reduce the response of the pituitary-adrenal axis to stress. It also causes gastric irritation.</p>
<p><b>PREDNISOLONE</b></p>		Corticosteroid

<p><b>PREDNISOLONE</b></p>		Corticosteroid
<p><b>INDICATIONS</b> Malignancies and cluster headache.</p> <p><b>MECHANISM OF ACTION</b> It is a short-acting natural glucocorticoid with mineralocorticoid activity.</p> <p><b>DOSAGE</b> PO: Dose varies according to indication. Adults: 10-60 mg/day. Children: 1-2 mg/kg/day divided in 4-6 doses. The dose is to be individualized. IM or IV: methylprednisolone sodium succinate: 10-40 mg slow IV followed by slow IM or IV (e.g. 30 mg/day IV over 10-20 mins).</p>	<p>Repeat if required 4-6 times a day, usually upto 2-3 days. Children: 0.5 mg/kg/day or more.</p> <p><b>CONTRAINDICATIONS</b> Systemic infection, live virus vaccination and hypersensitivity.</p> <p><b>DRUG INTERACTIONS</b> Decreases effect with anti-epileptics including carbamazepine, phenytoin, phenobarbitone. Some vaccines may cause serious reactions. ↓ actions of insulin, other antidiabetic drugs, anti-hypertensive agents.</p>	<p><b>ADVERSE EFFECTS</b> Indigestion, acne, weight gain, muscle weakness, mood changes/depression and bloody/black stools.</p> <p><b>SPECIAL PRECAUTIONS</b> Use cautiously in peptic ulcer, glaucoma, tuberculosis, depression, infection, diabetes, osteoporosis and with other medications. Prolonged use advocated only under strict supervision. Increased likelihood of adverse effects in elderly so reduced dose may be necessary.</p>

## ► MISCELLANEOUS DRUGS &gt; BISPHOSPHONATES

ZOLEDRONIC ACID		Bisphosphonate
<p><b>INDICATIONS</b> Hypercalcemia of malignancy, multiple myeloma and bone metastases from solid tumors.</p> <p><b>MECHANISM OF ACTION</b> It is a biphosphoric acid that is an inhibitor of osteoclastic bone resorption.</p> <p><b>DOSAGE</b> Administration: 4 mg is diluted in 100 ml of sterile 0.9% NaCl or 5% dextrose injection for intravenous infusion over no less than 15 minutes.</p> <p><b>DRUG INTERACTIONS</b> Increased risk of hypocalcemia when used in combination with loop diuretics. Risk of renal dysfunction may be increased when used in combination with thalidomide.</p> <p><b>ADVERSE EFFECTS</b> Electrolyte disturbances, anemia, weight loss, dyspnea, conjunctivitis, influenza-like symptoms, myalgia, arthralgia, fever, CNS effects, pruritus, rash, peripheral edema, hypertension and bradycardia.</p> <p><b>SPECIAL PRECAUTIONS</b> Monitor serum creatinine, calcium, electrolytes, phosphate, magnesium and hematocrit/hemoglobin. Adequately rehydrate the patient before treatment. Use with caution in hepatic insufficiency and asthma (aspirin sensitive).</p>		

**PAMIDRONATE**

Bisphosphonate

**INDICATIONS**

Hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, and osteolytic lesions of multiple myeloma.

**MECHANISM OF ACTION**

Pamidronate inhibits bone resorption both in vivo and in vitro. The main effect is on the osteoclast. The mechanism of action involves a number of processes. There is a direct toxic effect of ingested bisphosphonate on the resorbing osteoclast and with amino-substituted bisphosphonates particularly, there is inhibition of differentiation of osteoclast precursors to mature osteoclasts. It also disturbs the chemotactic gradient between bone and osteoclasts or interference with

the recognition and attachment of mature osteoclasts to the bone surface.

**DOSAGE**

*Hypercalcemia of malignancy:* Treatment would depend on the severity as well as symptoms of hypercalcemia. In mild hypercalcemia, vigorous saline hydration alone may be sufficient. The recommended dose of pamidronate in moderate hypercalcemia (corrected serum calcium of approx. 12 to 13.5 mg/dl) is 15-90 mg. The 60 mg dose is given as an initial, single dose intravenous infusion over 24 hrs. In severe hypercalcemia (Corrected serum calcium of approx. >13.5 mg/dl) is 90 mg. The 90 mg dose must be given as an initial single dose intravenous infusion over 24 hrs.

**CONTRAINDICATIONS**

Patients with clinically significant hypersensitivity to pamidronate or other bisphosphonates.

**ADVERSE EFFECTS**

Fluid overload, generalized pain, hypertension, abdominal pain, anorexia, constipation, nausea, vomiting, urinary tract infection, bone pain, anemia, hypokalemia, hypomagnesemia and hypophosphatemia.

**SPECIAL PRECAUTIONS**

Standard hypercalcemia related metabolic parameters such as serum levels of calcium, phosphate, magnesium, and potassium should be carefully monitored.

## ► MISCELLANEOUS DRUGS &gt; RADIOPHARMACEUTICALS

**STRONTIUM**

Radiopharmaceutical

**INDICATION**

Strontium chloride (<sup>89</sup>Sr) 89 is used to help relieve the bone pain that may occur with certain kinds of cancer. The radioactive strontium is taken up in the bone cancer area and gives off radiation that helps provide relief of pain. The presence of bone metastases should be confirmed prior to therapy.

**MECHANISM OF ACTION**

Soluble strontium compounds act like their calcium analogs, clearing rapidly from the blood and selectively localizing in bone mineral. Uptake of strontium by bone occurs preferentially in sites of active osteogenesis; thus primary

bone tumors and areas of metastatic involvement (blastic lesions) can accumulate significantly greater concentrations of strontium than surrounding normal bone

**DOSAGE**

The recommended dose of strontium chloride is 148 MBq, 4 mCi, administered by slow intravenous injection (1-2 minutes). Alternatively, a dose of 1.5-2.2 MBq/kg, 40-60 µCi/kg body weight may be used.

**CONTRAINDICATIONS**

Pregnancy, lactation, children under 18 years, patient suffering from Paget's disease or kidney disease.

**DRUG INTERACTION**

Antacids interacts with strontium. Antibiotics (quinolone, tetracycline antibiotics), estrogen and male hormones interact with strontium.

**ADVERSE EFFECTS**

Increased pain starting 2 to 3 days after treatment and lasting 2 to 3 days, flushing, diarrhea, fatigue, unusual bruising or bleeding, no decrease in pain 7 days after treatment, fever and chills.

**SPECIAL PRECAUTION**

Not to be used in cancer other than bone and clotting disorders.

**Durogesic®**

fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**

Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**

(Tramadol 37.5 mg + Paracetamol 325 mg)

## ► MISCELLANEOUS DRUGS &gt; ANTICONVULSANTS

CARBAMAZEPINE		Anticonvulsant
<b>INDICATIONS</b> Neuropathic pain, trigeminal neuralgia and idiopathic glossopharyngeal neuralgia.		
<b>MECHANISM OF ACTIONS</b> It reduces polysynaptic responses and blocks post-tetanic potentiation. Carbamazepine reduces pain in trigeminal neuralgia and glossopharyngeal neuralgia.	<b>CONTRAINDICATIONS</b> Hypersensitivity, AV block, AV conduction abnormality, bone marrow depression and porphyria.	<b>ADVERSE EFFECTS</b> Rash, blurred vision, dizziness/unsteadiness, nausea/loss of appetite, drowsiness and ankle swelling.
<b>DOSAGE</b> Adults: 100-200 mg. OD-BD: Increasing slowly to usually 800-1200 mg/day.	<b>DRUG INTERACTIONS</b> Carbamazepine reduces anticoagulant activity. OCP failure resulting in pregnancy can occur in concomitant use of oral contraceptive pills (OCP) with carbamazepine. Along with MAOIs, serious arrhythmia can occur. ↑ dose with phenytoin, phenobarbitone and primidone. It shortens doxycycline t½. Neurotoxicity with lithium. Cimetidine, verapamil ↑ carbamazepine effects.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in long standing hepatic/renal impairment, cardiac dysfunction, in other medications and history of hematological and reaction to other drugs. It may cause confused or agitated behavior in the elderly hence reduced dose may be necessary. The drug passes into breastmilk. Alcohol may increase the sedative effects of this drug.

GABAPENTIN		Anticonvulsant
<b>INDICATION</b> Adjuvant analgesic for cancer-related neuropathic pain.		
<b>MECHANISM OF ACTION</b> It enhances gamma amino butyric acid (GABA) release but is not an agonist at GABA receptors.	<b>CONTRAINDICATION</b> Hypersensitivity.	<b>ADVERSE EFFECTS</b> Somnolence, dizziness, ataxia, fatigue, nystagmus, headache, tremors, diplopia, nausea/vomiting and rhinitis.
<b>DOSAGE</b> Adults: 100 – 300 mg on day 1, 300 mg BID on 2 <sup>nd</sup> day, 300 mg TID on 3 <sup>rd</sup> day and then increased according to response, upto	<b>DRUG INTERACTIONS</b> Decreased gabapentin absorption and bioavailability with antacids. Gabapentin causes ↑ in phenytoin levels and its toxicity. Cimetidine may ↓ gabapentin clearance.	<b>SPECIAL PRECAUTIONS</b> Avoid sudden withdrawal (taper over a period of one week). Renal impairment. Driving or operating heavy machinery. The dose may have to be reduced in geriatric patients. Alcohol may cause an increase in the CNS depression.



**Durogesic®**

fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

60

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**ULTRACET®**

(Tramadol 37.5 mg + Paracetamol 325 mg)

**PHENYTOIN**

Anticonvulsant

**INDICATIONS**

Trigeminal neuralgia and migraine.

**MECHANISM OF ACTION**

It stabilizes threshold for hyperexcitability and reduces post tetanic potentiation at synapses.

**DOSAGE**

Adults: 100 mg BID/TID with or after meals. Max.: 600 mg/day. Inj.: 250-500 mg. IV slowly (not exceeding 50 mg/min.) OR 3-10 mg/kg body weight. Children: 4-7 mg/kg in divided doses. Max: 300 mg/day.

**CONTRAINDICATIONS**

Hypersensitivity, sinus bradycardia, sinoatrial block, Stokes-Adam syndrome and porphyria.

**DRUG INTERACTIONS**

Phenytoin cause ↓ in t<sub>1/2</sub> of dicoumarol and dexamethasone. ↓ dose with carbamazepine, doxazepam, diazepam, ethosuximide, valproate, anticoagulants, sulphonamides, INH, TCAs, disulfiram, chlorpromazine, furosemide, phenylbutazone, propanolol. ↑ dose with phenobarbitone, primidone, carbamazepine, clonazepam, digitalis, doxycycline, pyridoxine and steroids. It decreases blood levels of phenobarbitone, primidone, carbamazepine, clonazepam, digoxin, OCP, corticosteroids.

**ADVERSE EFFECTS**

Dizziness/headache, confusion, nausea/vomiting, insomnia, hypertrophy of gums, hirsutism, rash, CVS and CNS depression, arrhythmias, hypotension and circulatory collapse.

**SPECIAL PRECAUTIONS**

Use cautiously in chronic hepatic/renal impairment, diabetes, porphyria, other medications, hypotension, heart failure. Reduced dose may be necessary in geriatric and pediatric patients. It may cause the 'fetal hydantoin syndrome' if given to pregnant females. The drug passes into breast milk. Alcohol may alter the effects of this drug.

**PREGABALIN**

Anticonvulsant

**INDICATIONS**

Neuropathic pain and fibromyalgia.

**MECHANISM OF ACTION**

It enhances gamma amino butyric acid (GABA) release but is not an agonist at GABA receptors.

**DOSAGE**

**Neuropathic pain:** Initial: 150 mg/day, may increase to 300 mg/day after 3-7 days. Max: 600 mg/day after a 7-day interval. **Fibromyalgia:** Initial: 150 mg/day, may increase to 300 mg/day after a week. Max: 450 mg/day, if needed. All doses to be given in 2 or 3 divided doses.

**CONTRAINDICATION**

Hypersensitivity.

**DRUG INTERACTIONS**

May potentiate the effects of lorazepam. Additive CNS

depressant effects with opiates and benzodiazepines. May increase risk of angioedema with ACE inhibitors. May increase risk of weight gain and peripheral edema with thiazolidinediones.

**ADVERSE EFFECTS**

Somnolence, dizziness, headache, diplopia, blurred vision, vertigo, fatigue, irritability, arthralgia, muscle cramp, back and limb pain, cervical spasm, disorientation, insomnia, nasopharyngitis, ataxia, tremor, dysarthria, amnesia, paresthesia, hypoesthesia, lethargy, sedation, edema, peripheral edema, dry mouth, constipation, diarrhea, vomiting, nausea, flatulence, abdominal distension, increased appetite, weight gain, euphoria, confusion, reduced libido, erectile

dysfunction; attention, memory, coordination and gait disturbances; fall, feeling drunk, abnormal feeling. Rarely, Stevens-Johnson syndrome, rhabdomyolysis, breast enlargement, gynecomastia and angioedema.

**SPECIAL PRECAUTIONS**

Patient with history of angioedema episodes, severe CV disease, renal impairment. Avoid abrupt withdrawal. Pregnancy and lactation. Patient counselling may impair ability to drive, operate machinery or engage in hazardous activities. Monitor blood parameters, monitor visual disturbances. Closely observe for clinical worsening, suicidality and unusual changes in behavior.

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VALPROIC ACID	!  X	Anticonvulsant
<b>INDICATION</b> Neuropathic pain.	<b>DRUG INTERACTIONS</b> ↓ dose with phenobarbitone, primidone and methyl phenobarbitone and aspirin. ↑ dose with carbamazepine, phenytoin. Use cautiously with anticoagulants.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in impaired renal function, major surgery, hepatic disease (increases bleeding time) do frequent LFT every 6 months. Sodium valproate gives a false positive urine test for ketones. Avoid abrupt withdrawal. Reduced dose necessary in pediatric and geriatric patients. Alcohol increases the sedative effect.
<b>MECHANISM OF ACTION</b> It causes increase in brain levels of GABA.	<b>ADVERSE EFFECTS</b> Drowsiness, vertigo, alopecia (reversible), skin rash, thrombocytopenia, weight gain, fulminant hepatitis, hepatotoxicity (mostly in children and polypharmacy).	
<b>DOSAGE</b> Adults: Initially 600 mg daily in two divided doses, increasing by 200 mg at 3 day intervals. Maintain: 1-2 gm/day. Max: 2-5 gm/day. Effective dosing range: 500 mg-1000 mg t.i.d.		
<b>CONTRAINDICATIONS</b> Hepatic disease, hypersensitivity, concomitant use of clonazepam.		

## ► MISCELLANEOUS DRUGS > ANESTHETICS

CAPSAICIN	!  X	Anesthetic
<b>INDICATION</b> Pain.	<b>DOSAGE</b> Topical application: 3-4 times daily, also available in patch.	containing zucapsaicin while using capsaicin.
<b>MECHANISM OF ACTION</b> Capsaicin works by decreasing a certain natural substance in the body (substance P) that helps pass pain signals to the brain. Thus, decreases pain perception.	<b>CONTRAINDICATIONS</b> Not specified.	<b>ADVERSE EFFECTS</b> Warmth, stinging, or burning on the application site may occur
	<b>DRUG INTERACTION</b> Before using capsaicin inform if using class I antiarrhythmic drugs. Avoid use of medications	<b>SPECIAL PRECAUTIONS</b> Avoid the use of the drug if serious allergic reaction occurs although rare. Avoid inhalation of the residue.

LIDOCAINE	!  !	Anesthetic
<b>INDICATION</b> Neuropathic pain.	<b>CONTRAINDICATIONS</b> Hypersensitivity, conduction disturbances, AV block, cardiac decompensation.	<b>ADVERSE EFFECTS</b> Respiratory depression, cardiovascular collapse, cardiac arrest. These symptoms may occur quietly without any warning. Convulsions, Tremors, dizziness, blurred vision, nervousness and nausea may occur. Skin irritation, rash, redness.
<b>MECHANISM OF ACTION</b> It stabilizes the neuronal membrane and inhibits the ion movement which is necessary for conduction of impulses. It reduces phase IV and depolarization and decreases automaticity.	<b>DRUG INTERACTIONS</b> ↓ dose required with cimetidine, propanolol. Concurrent use with suxamethonium results in increased duration of suxamethonium activity. Adrenaline given along with lignocaine prolongs its local action by reducing its absorption. Although limited absorption, not to be used with class I anti-arrhythmics.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in severe liver disease, epilepsy, bradycardia, neonates, impaired cardiac conduction, pregnancy and lactation.
<b>DOSAGE</b> 5% lidocaine gel or patch: Place over skin on painful region for 12 hours/day. 1-3 patches over 24 hours.		



**Durogesic®**

Fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**

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(Tramadol 37.5 mg + Paracetamol 325 mg)

► MISCELLANEOUS DRUGS > ANTIDEPRESSANTS

## AMITRIPTYLINE



Antidepressant

### INDICATIONS

Chronic pain and adjuvant analgesic for cancer pain and depression.

### MECHANISM OF ACTION

It blocks the neuronal reuptake of noradrenaline and serotonin. Amitriptyline has some sedative action. It has anticholinergic actions also.

### DOSAGE

Adults: Initially 75 mg, gradually ↑ upto 150 mg/day (in divided doses). Maintenance dose: 50-100 mg/day. Cancer pain: 25-100 mg PO.

### CONTRAINDICATIONS

Hypersensitivity, ischemic heart disease, cardiovascular insufficiency,

retention of urine. Manic phase, severe lung disease, MAOIs, lactation and pregnancy.

### DRUG INTERACTIONS

↓ dose with antiparkinsonism drugs, Sympathomimetics, neuroleptics, ↑ dose with barbiturates.

Concomitantly used antihypertensives need to be given in increased dosage. Alcohol potentiates the sedative effects. Severe fatal reaction can occur with MAOIs, so avoid their concomitant use.

### ADVERSE EFFECTS

Ventricular fibrillation, postural hypotension, dry mouth, difficulty in passing urine, drowsiness, pal-

pitations, agranulocytosis, thrombocytopenia, arrhythmias, tremors, dizziness/fainting, sweating, blurred vision, headache, constipation, confusion and delirium, weight gain and sexual disturbances.

### SPECIAL PRECAUTIONS

Use cautiously while driving / operating heavy machinery, in bipolar illness, cardiac/hepatic/ renal/thyroid/prostate disease, conduction abnormalities, epilepsy, glaucoma, psychosis, chronic alcoholics. Reduce dose in elderly.

## NORTRIPTYLINE



Antidepressant

### INDICATIONS

Neurogenic pain, urticaria/nausea, vomiting during chemotherapy and depression.

### MECHANISM OF ACTION

It is not known whether nortriptyline inhibits the activity of histamine, 5-HT and acetylcholine. It interferes with transport, release and storage of catecholamines.

### DOSAGE

50-150 mg single/divided doses. Children: 8-11 yrs: 10-20 mg/day, > 11yr: 25-35 mg/day given at bedtime with food (to lower GI irritation). treatment not to exceed 3 months.

### CONTRAINDICATIONS

Hypersensitivity, mania, epilepsy, urinary retention, acute MI, narrow angle glaucoma. Lactation, children below 6 years and neonates.

### DRUG INTERACTIONS

↓ dose required with cimetidine, sympathomimetics, phenytoin. MAOIs may cause hyperpyrexia on concomitant use. Stop MAOIs at least 2 weeks prior to the treatment. ↑ in anticoagulant activity of coumarins on concomitant use. Phenothiazine raises blood levels. Interferes with anticonvulsant control.

### ADVERSE EFFECTS

Tachycardia, arrhythmias, blurred vision, skin rash, jaundice, dry mouth, constipation, nausea, urinary hesitancy, epigastric discomfort, peripheral neuropathy, sedation, confusion and cholestatic jaundice rarely.

### SPECIAL PRECAUTIONS

Use in schizophrenics may cause exacerbation of the psychosis. In MDP patients manic episode may be precipitated. Seizures can also occur with its use. Reduced dosage is necessary as adverse effects especially the cardiotoxicity and psychiatric effects occur with increased frequency in elderly.

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fentanyl transdermal system  
12 mcg/hr, 25 mcg/hr, 50 mcg/hr

## PRELOGIC™

Pregabalin 75mg + Methylcobalamin 750mcg

## ULTRACET®

(Tramadol 37.5 mg + Paracetamol 325 mg)

**PAROXETINE**

Antidepressant

**INDICATIONS**

Pain and depression.

**MECHANISM OF ACTION**

It is an orally administered serotonin selective reuptake inhibitor.

**DOSAGE**

Initially 20 mg daily, increased gradually, if necessary to 50 mg daily.

**CONTRAINDICATIONS**

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs).

**DRUG INTERACTIONS**

Monoamine oxidase inhibitors, warfarin, drugs affecting hepatic metabolism, tricyclic antidepressant (TCA) and alcohol.

**ADVERSE EFFECTS**

Asthenia, sweating, nausea, decreased appetite, somnolence,

dizziness, insomnia, tremor, nervousness, constipation, ejaculatory disturbance, and impotence.

**SPECIAL PRECAUTIONS**

Use cautiously in patients with a history of mania and seizures. Close supervision of high risk patients with suicidal tendencies and patients with severe renal or severe hepatic impairment. Avoid operating hazardous machinery, including automobiles.

## ► MISCELLANEOUS DRUGS &gt; NON-OPIOID THERAPY

**ACETAMINOPHEN**

Non-opioid therapy

**INDICATIONS**

Pain and fever.

**MECHANISM OF ACTION**

It blocks prostaglandin synthesis by cyclo-oxygenase pathway.

**DOSAGE**

1-4 gm daily.

**CONTRAINDICATIONS**

Liver failure, hypersensitivity.

**DRUG INTERACTIONS**

↑ absorption of cholestyramine, pethidine, propantheline. ↑ effect of anticoagulants. ↑ side effects of zidovudine. ↑ levels with metoclopramide. Alcohol potentiates hepatotoxicity.

**ADVERSE EFFECTS**

Nausea, vomiting, rash, leucopenia, liver damage following overdose.

**SPECIAL PRECAUTIONS**

Use cautiously in renal and hepatic impairment, analgesic nephropathy. Reduced dose necessary up to 12 years.

## ► MISCELLANEOUS DRUGS &gt; NSAIDS

**ASPIRIN**

NSAID

**INDICATIONS**

Pain, fever and myalgia.

**MECHANISM OF ACTION**

It blocks prostaglandin synthesis by cyclo-oxygenase pathway.

**DOSAGE**Adults: *Analgesic/antipyretic:* 300-500 mg TID. To be taken with food or milk.**CONTRAINDICATIONS**

Hypersensitivity, gout, GI bleeding, asthma, hemophilia.

**DRUG INTERACTIONS**

Anticoagulants: ↑ anticoagulant action, abnormal bleeding. Other NSAIDs cause ↑ in likelihood of stomach irritation. Oral hypoglycemic agents potentiate hypoglycemic action. Drugs for gout ↓ effects especially probenecid and sulfapyrazone.

**ADVERSE EFFECTS**

Rash, ringing in the ears, indigestion, breathlessness, wheezing, nausea/vomiting, epigastric distress, GI irritation with

slight asymptomatic blood loss, increased bleeding time, Reye's syndrome, cerebral hemorrhage in patients with preexisting lesions.

**SPECIAL PRECAUTIONS**

Use cautiously in peptic ulceration, hemorrhagic diathesis, cerebrovascular hemorrhage, chronic hepatic or renal disorder, platelet disorders, hemophilia, hypoprothrombinemia. Avoid prolonged use unless specifically indicated. Increases the likelihood of stomach irritation with alcohol.

DICLOFENAC	! ☰ x !	NSAID
<p><b>INDICATION</b> Pain.</p> <p><b>MECHANISM OF ACTION</b> It is an inhibitor of cyclooxygenase pathway of prostaglandin synthesis.</p> <p><b>DOSAGE</b> Adults: 75 mg/day in 2-3 divided doses. Maintenance dose: 50-100 mg/day in divided doses. Children: 1-12 yrs: 1-3 mg/kg/day in divided doses.</p>	<p><b>CONTRAINDICATIONS</b> Active peptic ulcer, GI bleeding, NSAID induced allergic asthma.</p> <p><b>DRUG INTERACTIONS</b> Oral anticoagulants, corticosteroids, other NSAIDs. Aspirin: Risk of peptic ulcer bleeding. Indigestion remedies: disrupt the enteric coating. Antihypertensive drugs and diuretics: reduced beneficial effects of this drug. Cyclosporine: renal adverse effects.</p>	<p><b>ADVERSE EFFECTS</b> Gastrointestinal disorders, headache/dizziness, drowsiness, swollen feet/ankles, rash, wheezing/breathlessness. GI bleeding.</p> <p><b>SPECIAL PRECAUTIONS</b> Use cautiously in chronic hepatic or renal dysfunction, hypertension, bleeding disorder, peptic ulcer or esophagitis, porphyria, allergy to aspirin, asthma and in other medications.</p>

ETODOLAC	! x ☰ x !	NSAID
<p><b>INDICATION</b> Pain.</p> <p><b>MECHANISM OF ACTION</b> The mechanism of action of etodolac, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.</p> <p><b>CONTRAINDICATIONS</b> Known hypersensitivity to etodolac; patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.</p> <p><b>DOSAGE</b> Analgesia: Up to 1000 mg, given as 200-400 mg every 6 to 8 hours.</p> <p><b>DRUG INTERACTIONS</b> NSAIDs may diminish the antihypertensive effect of ACE-inhibitors;</p>	<p>when etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. Other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of cyclosporine, digoxin, methotrexate, and increased toxicity; the effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone.</p> <p><b>ADVERSE EFFECTS</b> Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/</p>	<p>duodenal), vomiting, abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.</p> <p><b>SPECIAL PRECAUTIONS</b> Patients receiving etodolac who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored. Etodolac should not be administered to patients with aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.</p>

**FENOPROFEN**

NSAID

**INDICATION**

Pain.

**MECHANISM OF ACTION**

Inhibition of cyclooxygenase activity and prostaglandin synthesis.

**DOSAGE**

Oral: 200 mg every 4 to 6 hr as needed.

**CONTRAINDICATIONS**

History of significantly impaired renal function; hypersensitivity to fenoprofen; asthma, urticaria, or allergic-type reactions after taking

aspirin or other NSAIDs; Patients who have undertaken treatment for perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

**DRUG INTERACTION**

NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. Coadministration of aspirin decreases the biologic half-life of fenoprofen. Reduce the natriuretic effect of furosemide and thiazides in some patients. Inhibits lithium clearance.

**ADVERSE EFFECTS**

Palpitation, headache, dizziness, increased sweating, pruritus, rash, tinnitus, blurred vision, dyspepsia and upper respiratory tract infection.

**SPECIAL PRECAUTIONS**

Patients with CV disease or risk factors for CV disease may be at greater risk, elderly, breast feeding mothers, pregnancy, patients with fluid retention, heart failure, or hypertension.

**IBUPROFEN**

NSAID

**INDICATIONS**

Pain, fever and musculoskeletal disorders.

**MECHANISM OF ACTION**

It is an inhibitor of cyclooxygenase pathway of prostaglandin synthesis.

**DOSAGE**

*Adults:* 400-600 mg daily (general pain relief). *Children:* analgesic/antipyretic: 10-15 mg/kg/dose every 4-6 hrs. Not recommended in children under 7 kg.

**CONTRAINDICATIONS**

Peptic ulcer, active GI bleeding, history of hypersensitivity

precipitated by aspirin or other NSAIDs.

**DRUG INTERACTIONS**

Oral anticoagulants, corticosteroids, other nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin: ↑ risk of bleeding and/or peptic ulcers. Antihypertensive drugs and diuretics: Reduced beneficial effects of these drugs. Lithium: raised blood lithium levels.

**ADVERSE EFFECTS**

Nausea/vomiting, heartburn/indigestion, rash, wheezing/breathlessness, headache, vomiting, jaundice and GI intolerance.

**SPECIAL PRECAUTIONS**

Use cautiously in chronic renal dysfunction. Hypertension, peptic ulcer, esophagitis or acid indigestion, asthma and in other medications. Reduced dose may be necessary in elderly and children. Avoid alcohol due to risk of gastric irritation with ibuprofen.

**INDOMETACIN**

NSAID

**INDICATIONS**

Pain, musculoskeletal disorders.

**MECHANISM OF ACTION**

It is an inhibitor of cyclo-oxygenase pathway of prostaglandin synthesis. It closes PDA by inhibition of PG synthesis.

**DOSAGE**

*Adult:* Oral: 50-200 mg daily in divided doses with food.

**CONTRAINDICATIONS**

Hypersensitivity, active GI bleeding, asthma induced by aspirin, or other NSAIDs.

**DRUG INTERACTIONS**

↑ risk of bleeding and/or peptic ulcer. Oral anticoagulants, corti-

costeroids, other NSAIDs, aspirin: lithium: ↑ lithium levels. ↓ effects of antihypertensive drugs and diuretics. Probenecid: raised probenecid blood levels.

**ADVERSE EFFECTS**

Abdominal pain/indigestion, headache, dizziness, light headedness, nausea/vomiting, diarrhea, drowsiness/depression, blurred vision, rash, wheezing/breathlessness.

**SPECIAL PRECAUTIONS**

Use cautiously in chronic hepatic or renal dysfunction, peptic ulcer, esophagitis or acid indigestion, Cardiac disorders, hypersensitivity, epileptic fits, asthma, bleeding

disorders and in other medications. During prolonged therapy, ophthalmic and blood exam required. Not usually prescribed for children under 14 except in patent ductus arteriosus in neonates. Reduced dose is necessary. Likelihood of adverse effects in elderly, so not usually prescribed. It may affect the unborn baby, and taken in late pregnancy may prolong labour. The drug passes into breastmilk and may affect the baby. May increase the risk of stomach irritation.

KETOROLAC		NSAID
<b>INDICATION</b> Pain.		
<b>MECHANISM OF ACTION</b> It decreases prostaglandin synthesis.	<b>CONTRAINDICATIONS</b> Coagulation disorders, peptic ulcers, hypersensitivity, angioedema, nasal polyp and moderate or severe renal impairment.	<b>ADVERSE EFFECTS</b> Nausea, peptic ulceration, GI bleed, drowsiness, dizziness, diarrhea, Stevens-Johnson syndrome, flushing, palpitation, vertigo, constipation, acute renal failure.
<b>DOSAGE</b> Adults: Injection: Initially 30-60 mg by IM then 10-30 mg every 4-6 hrs. IM: Maximum dose: 60 mg/day. Tablets: Orally 20 mg initially followed by 10 mg/4-6 hrs. Maximum dose: 40 mg/day. (Treatment not to exceed 5 days).	<b>DRUG INTERACTIONS</b> Methotrexate causes delayed ketorolac excretion, which could prove fatal. Furosemide causes ↓ diuretic response, ↑ K <sup>+</sup> excretion. Other NSAIDs side effects. Probenecid cause ↓ in ketorolac excretion. Morphine causes ↑ in analgesia. Salicylates ↑ plasma ketorolac levels.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in hepatic and renal dysfunction, GI disease, Hypersensitivity to aspirin or other NSAIDs, hypovolemia dehydration. Reduced dose necessary in elderly. Increased risk of GI irritation with alcohol.

NABUMETONE		NSAID
<b>INDICATIONS</b> Pain and inflammation.		
<b>MECHANISM OF ACTION</b> Nabumetone is a weak cyclooxygenase (COX) inhibitor and is converted in the liver to 6-methoxy-2-naphthalacetic acid (6-MNA), a potent inhibitor of COX, the enzyme responsible for prostaglandin synthesis. This results in the reduction of prostaglandin levels and alleviation of pain and inflammation.	<b>CONTRAINDICATIONS</b> trimester), lactation. Perioperative pain in the setting of CABG.	<b>ADVERSE EFFECTS</b> headache, tinnitus, dizziness; rash, pruritus; constipation; edema; insomnia, fatigue, nervousness, somnolence; diaphoresis. Potentially fatal: Exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Severe hepatic reactions (e.g. fulminant hepatitis, liver failure). Anaphylactoid reactions.
<b>DOSAGE</b> Adult: Oral: 1 g as a single dose in the evening, followed by 0.5-1 g in the morning if necessary.	<b>DRUG INTERACTIONS</b> Antihypertensive effects of hypotensive agents may be reduced; cyclosporine levels ↑; seizures risk ↑ with fluoroquinolones; May ↓ efficacy of diuretics. May diminish the cardioprotective effect of acetylated salicylates. Alcohol may enhance gastric mucosal irritation. Potentially Fatal: GI ulceration ↑ with corticosteroids; with lithium toxicity ↑; Severe bone marrow suppression, aplastic anemia and GI toxicity with methotrexate; ↑ bleeding with anticoagulants and antiplatelet agents; absorption ↓ with colestyramine (and other bile acid sequestrants).	<b>SPECIAL PRECAUTIONS</b> Pre-existing CV risk factors or disease; fluid retention, CHF, hypertension. History of GI disease (bleeding or ulcers). Elderly or debilitated patients. Other forms of asthma. Hepatic impairment; closely monitor patients with any abnormal LFT. Renal impairment; rehydrate patient prior to therapy and closely monitor renal function. Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

**NAPROXEN SODIUM**

NSAID

**INDICATION**

Pain.

**MECHANISM OF ACTION**

It is an inhibitor of cyclooxygenase pathway of prostaglandin synthesis.

**DOSAGE**

*Mild to moderate pain:* 500 mg (starting dose), then 250 mg every 6-8 hrs. as required. *Muscular pain:* 500-1250 mg daily.

**CONTRAINDICATIONS**

Peptic ulcers, active GI bleeding.

**DRUG INTERACTIONS**

*Lithium:* altered blood lithium levels. *Antihypertensive drugs, diuretics:* ↑ effects of oral anticoagulants,

*Phenytoin, methotrexate, sulphonamides, hypoglycemics. Probenecid:* increased serum naproxen concentration.

**ADVERSE EFFECTS**

Gastrointestinal disorders, headache, inability to concentrate, ringing in the ears, swollen feet/ankles, rash/itching, wheezing/breathlessness.

**SPECIAL PRECAUTIONS**

Use cautiously in hepatic or renal dysfunction, hypertension, heart problems, bleeding disorder, peptic ulcer, esophagitis or acid indigestion, salicylate sensitivity, asthma and with other medications. Not recommended below age 2

years. Likelihood of adverse effects. Reduced dose may therefore be necessary. Not usually prescribed during labour. It may increase the risk of adverse effects on the infant's heart and may prolong labour. The drug passes into breast milk, but at normal doses adverse effects on the baby are unlikely. Keep the consumption low. Alcohol may increase the risk of stomach irritation.

**PIROXICAM**

NSAID

**INDICATION**

Pain.

**MECHANISM OF ACTION**

It is an inhibitor of cyclooxygenase pathway of prostaglandin synthesis.

**DOSAGE**

Adults: 20 mg. OD/BD for 7-14 days.

**CONTRAINDICATIONS**

Recurrent peptic ulcer, active peptic ulcer, NSAID induced allergies, hypersensitivity, bronchial asthma.

**DRUG INTERACTIONS**

*Diuretics:* risk of renal damage. *Aspirin:* reduced serum piroxicam levels. *Corticosteroids, oral anticoagulants and NSAIDs:* risk of bleeding. *Lithium:* serum lithium levels. *Antihypertensives:* reduced piroxicam beneficial effects.

**ADVERSE EFFECTS**

Edema, vomiting, nausea, heartburn, epigastric distress, tinnitus, skin rash.

**SPECIAL PRECAUTIONS**

Use cautiously in severe impairment of renal and hepatic function, hypertension, surgery, hemorrhagic disorders, cardiovascular diseases and in prolonged use. Not recommended in age below 6 years. Reduced dose necessary in elderly due to increased likelihood of adverse effects.

**SULINDAC**

NSAID

**INDICATIONS**

Sulindac is a nonsteroidal anti-inflammatory agent (NSAIA) of the arylalkanoic acid class. Possessing analgesic and antipyretic activities.

**MECHANISM OF ACTION**

Not specified.

**DOSAGE**

For symptomatic treatment: 150-200 mg bid; may adjust subsequent doses based on response. Max: 400 mg/day.

**CONTRAINDICATION**

Hypersensitivity. Pregnancy (3<sup>rd</sup> trimester), treatment of perioperative pain in CABG surgery.

**DRUG INTERACTIONS**

Concomitant use with dimethyl sulfoxide may result in peripheral neuropathy. Increased nephrotoxicity with cyclosporine;

increased risk of methotrexate toxicity; increased risk of bleeding with other NSAIDs, warfarin and thrombolytic agents. Antagonises effect of antihypertensives. Unpredictable interactions with lithium

**ADVERSE EFFECTS**

Headache, dizziness, nausea, vomiting, dyspepsia, GI cramps and pain, diarrhea, constipation, flatulence, anorexia, tinnitus, rash, pruritis, erythema multiforme, nervousness, edema, urine discoloration, muscle weakness, sore or dry mucous membranes, stomatitis, gastritis, peptic ulcer, GI bleeding, alopecia, photosensitivity, congestive heart failure, arrhythmia, hyperkalemia, thrombocytopenia, liver function abnormalities, pancreatitis, proteinuria, renal

calculi, hypersensitivity reactions, and hypersensitivity vasculitis.

**Severe:** Anaphylaxis reactions; cross-sensitivity reactions in patients with known aspirin triad reactions; Stevens-Johnson Syndrome and toxic epidermal necrolysis.

**SPECIAL PRECAUTIONS**

Use at lowest effective dose for shortest duration possible. NSAIDs may increase risk of severe cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Risk may be increased with duration of use or pre-existing CV disease or risk factors. GI disturbances and bleeding disorders.

**TOLMETIN SODIUM**

NSAID

**INDICATION**

Pain.

**MECHANISM OF ACTION**

Decreases inflammation, pain, and fever, probably through inhibition of cyclooxygenase activity and prostaglandin synthesis.

**DOSAGE**

Oral 400 mg 3 times daily.

**CONTRAINDICATIONS**

Pregnancy (3<sup>rd</sup> trimester), hypersensitivity to aspirin and NSAIDs, treatment of perioperative pain in CABG surgery.

**DRUG INTERACTIONS**

Decreases the efficacy of mifepristone. Increased risk of bleeding with anticoagulants,

other NSAIDs, antiplatelets, LMWH. Increased risk of convulsions with quinolones. Decreased antihypertensive response to loop diuretics,  $\beta$ -blockers and ACE inhibitors. Coadministration increased plasma concentrations of lithium, methotrexate and cardiac glycosides. Increased risk of nephrotoxicity with ACE inhibitors, penicillamine, cyclosporine, tacrolimus or diuretics.

**ADVERSE EFFECTS**

Nausea, dyspepsia, diarrhea, flatulence, vomiting, headache, GI bleed, hypersensitivity reactions, asthenia, hypertension, edema, dizziness, weight gain, weight loss, visual disturbances, tinnitus, abnormal liver function. Erosive

esophagitis, interstitial nephritis and nephrotic syndrome.

**Potentially Fatal:** Blood dyscrasias, serious CV thrombotic events, hepatitis, Stevens-Johnson syndrome.

**SPECIAL PRECAUTIONS**

Lactation, elderly. Impaired renal and hepatic function. CV diseases, fluid retention, heart failure, history of GI bleed or gastric ulcer, dehydration, hypertension. Monitor renal function regularly.

**Durogesic®**

fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**

Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**

(Tramadol 37.5 mg + Paracetamol 325 mg)

## ► MISCELLANEOUS DRUGS &gt; OPIOID THERAPIES

**FENTANYL**

Opioid therapy

**INDICATIONS**

It provides analgesia during short surgical procedures. It is used as premedication, during anesthetic period, induction and maintenance, and in the immediate postoperative period. In combination with a neuroleptic for inducing neuroleptanalgesia. It is given as a general anesthetic along with oxygen and muscle relaxants and as an adjunct to regional anesthesia.

**MECHANISM OF ACTION**

It is an exceptionally potent synthetic opioid and has rapid onset of effect with short duration. It exhibits typical opioid profile of analgesia and respiratory depression. It has minimal effects on cardiovascular system but induces muscle rigidity which can be abolished by naloxone or neuromuscular blockers.

**DOSAGE**

**Adult:** Buccal *Breakthrough cancer pain:* Patients already receiving and tolerant to opioid treatment: As loz: Initial: 200 mcg over 15 min per episode; may repeat once after 15 min if needed. Max: 1.6 mg/dose. No more than 4 unit doses should be taken daily. As tab: Initial: 100 mcg episode; may repeat once after

30 min if needed; wait for at least 2 or 4 hr before treating another episode. As film: Initial: 200 mcg per episode; thereafter, at least 2 hr must elapse before treating another episode. *Sublingual Breakthrough cancer pain:* As tab: Initial: 100 mcg per episode; may repeat once after 30 min if needed; wait for at least 2 or 4 hr before treating another episode. As spray: Initially, 100 mcg per episode; may repeat once after 30 min if needed; wait for at least 4 hr before treating another episode. IV *Adjunct to general anesthesia:* Patients w/ spontaneous respiration: Initial: 50-200 mcg followed by supplements of 50 mcg. Max: 200 mcg. Admin lower infusion rates of 0.05-0.08 mcg/kg/min. Patients w/ assisted ventilation: Initial: 300-3,500 mcg (up to 50 mcg/kg) followed by supplements of 100-200 mcg depending on response. Loading dose (alternatively via bolus): Approx 1 mcg/kg/min given for the 1st 10 min followed by infusion of approx 100 ng/kg/min. IM *Premedication before anesthesia:* 50-100 mcg to be given 30-60 min prior to induction of anesthesia. Transdermal *Intractable chronic pain opioid-naïve patients:* Initial: Apply

patch that delivers ≤25 mcg/hr. Adjust dose according to response. Patients receiving a strong opioid analgesic: Initial dose should be based on the previous 24-hr opioid requirements. Replace patch every 72 hr and apply the new patch to a different site; avoid using the same area of skin for a few days.

**CONTRAINDICATIONS**

Respiratory depression; raised intracranial pressure; hypovolemia /hypotension.

**DRUG INTERACTIONS**

CNS depressants such as benzodiazepines, barbiturates, tranquilizers and general anesthetics may have additive or potentiating effects. Atracurium and vecuronium may result in severe bradycardia.

**ADVERSE EFFECTS**

Others: nausea, bradycardia, hypotension, pruritus, urinary retention and seizures.

**SPECIAL PRECAUTIONS**

Muscle rigidity may worsen respiratory depression that persists for several hours, head injury, elderly, debilitated subjects: renal or hepatic impairment, pregnancy, lactation, neonates.

**BUPRENORPHINE**

Opioid therapy

**INDICATIONS**

Pain in cancer, premedication before surgery, post surgical period.

**MECHANISM OF ACTION**

It binds m-sub class of opioid receptors in CNS. It has long duration of action than morphine. Low abuse potential. Respiratory depression potential same as morphine.

**DOSAGE**

Sublingual *Moderate to severe pain:* 200-400 mcg 6-8 hrly. IV

*Perioperative analgesia:* 300-450 mcg via slow inj. IV/IM *Moderate to severe pain:* 300-600 mcg 6-8 hrly. IM *Anesthetic premedication:* 300 mcg.

**CONTRAINDICATIONS**

Hypersensitivity, severe respiratory disease.

**DRUG INTERACTIONS**

↓ dose with CNS depressants MAOIs. Benzodiazepines and other narcotics may precipitate withdrawal symptoms in narcotic addicts.

**ADVERSE EFFECTS**

Dizziness, sedation, miosis, respiratory depression, sweating, nausea/vomiting.

**SPECIAL PRECAUTIONS**

Use cautiously in hepatic dysfunction, depressed respiration during labour. Avoid driving and operating heavy machinery. Not recommended in children below 2 yrs. Use with caution in elderly- adverse effects may be increased. CNS depression increased with alcohol.

CODEINE			Opioid therapy
<b>INDICATIONS</b> Mild to moderate pain, symptomatic relief of diarrhea.	<b>CONTRAINDICATIONS</b> Hypersensitivity, liver disease, respiratory failure.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in chronic hepatic/renal dysfunction, asthma or bronchitis and in other medications. Reduced dose may be necessary in children and elderly. It should be avoided below 1 yr. The drug passes into breastmilk. May adversely affect the baby's breathing if taken during labour.	
<b>MECHANISM OF ACTION</b> It depresses cough centre but only 1/3 as potent as morphine.	<b>DRUG INTERACTIONS</b> Antidepressants, antipsychotics, sleeping drugs, antihistamines; added sedation with these drugs.		
<b>DOSAGE</b> Adult: PO Pain 15-60 mg 4 hrly. Max: 360 mg/day. Acute diarrhea: 15-60 mg 3-4 times daily. Syrup: 1-2.5 mL every 4-6 hr. IV/IM/SC Pain: 30-60 mg 4 hrly. Max: 240 mg/day.	<b>ADVERSE EFFECTS</b> Constipation, nausea/vomiting, drowsiness, dizziness, agitation/restlessness, rash/hives, wheezing/breathlessness, respiratory depression.		

HYDROMORPHONE			Opioid therapy
<b>INDICATION</b> Pain.	<b>CONTRAINDICATIONS</b> Give 1 to 2 mg intramuscularly or subcutaneously 6 hours as needed.	<b>SPECIAL PRECAUTIONS</b> because it may take away the analgesic effect of hydromorphone.	
<b>MECHANISM OF ACTION</b> It stimulates receptors on nerves in the brain to increase the threshold to pain (increasing the amount of stimulation it takes to feel pain) and reduce the perception of pain (the perceived importance of the pain).	<b>DRUG INTERACTION</b> Acute respiratory depression, obstructive airway diseases and acute alcoholism, raised intracranial pressure or head injury. Convulsive disorders, comatose patients. Patients on MAOI treatment or within 14 days of stopping such treatment.	<b>ADVERSE EFFECTS</b> Light headedness, dizziness, sedation, nausea and vomiting, constipation, sweating, flushing, itching, dry mouth, and respiratory dysfunction.	
<b>DOSAGE</b> Immediate-release tablets: Take 2 to 4 mg tablets by mouth every 4 to 6 hours as needed. Increase to 8 mg after careful observation and if needed to control pain. Extended-release tablets: Start after discontinuation of all other opioid extended-release tablets. Dosed once-daily, individualized based on prior opioid therapy. Injections:	<b>Hydromorphone should be used very cautiously with medications that depress the central nervous system (for example, hypnotics, anesthetics, tranquilizers, phenothiazines, and alcohol). And with mixed agonist/antagonist opioid analgesics (for example, pentazocine, nalbuphine, butorphanol, and buprenorphine)</b>	<b>SPECIAL PRECAUTIONS</b> Cautious about respiratory depression and abuse potential. Use with alcohol or other medications affecting central nervous system can worsen respiratory depression and may lead to death. Avoid its use in pregnant and nursing mothers.	

**METHADONE**

Opioid therapy

**INDICATION**

Pain, intractable cough associated with lung cancer.

**MECHANISM OF ACTION**

It is a mu-agonist; a synthetic opioid analgesic with multiple actions. It acts on the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction.

**DOSAGE**

Adult: Oral analgesia Initial: 2.5-10 mg 6-8 hrly if needed. Opioid dependence Individualize dose according to opiate tolerance. Usual regimen: Initial: 20-30 mg as a single dose. Additional doses of 5-10 mg may be used if withdrawal symptoms are not suppressed or if

they reappear. Max: 40 mg on the 1st day. Usual stabilizing dose: 40 mg/day in single or divided doses. Once patient has stabilized, reduce dosage gradually. Dosage must be individualized. Intractable cough associated with lung cancer: 1-2 mg 4-6 hrly, reduce to 12 hrly for prolonged use.

**CONTRAINDICATIONS**

Acute respiratory depression; acute bronchial asthma; acute alcoholism; risk of paralytic ileus; raised intracranial pressure or head injury.

**DRUG INTERACTIONS**

Withdrawal symptoms may be experienced with naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine. Increased clearance and possible reduced efficacy with

some antiretroviral agents.

**ADVERSE EFFECTS**

Nausea; vomiting; constipation; anorexia; abdominal pain; drowsiness; respiratory depression; hypotension; bradycardia; euphoria; headache; dysphoria; urinary retention; miosis; visual disturbances; impotence; dizziness; sweating; pruritus; asthenia; arrhythmias; QT prolongation. Potentially fatal: Cardiac arrest; respiratory arrest; shock

**SPECIAL PRECAUTIONS**

Dose should be individualized. Prolonged QT interval; CV disease; hepatic impairment; electrolyte abnormalities; concomitant use of QT prolonging drug; respiratory disease; elderly. Driving or operating any machinery should be avoided.

**MORPHINE**

Opioid therapy

**INDICATIONS**

Prolonged relief of severe and intractable pain.

**MECHANISM OF ACTION**

It acts at mu-subclass of opioid receptors. Analgesia, euphoria and dependence are due to action on m<sub>1</sub> receptors while respiratory depression and inhibition of intestinal movements is due to m<sub>2</sub> receptor action. Spinal analgesia is due to action on k-receptor. It suppresses cough centre. It adversely effects release of hormones.

**DOSAGE**

Adult: Moderate to severe pain: orally 5-20 mg, 4 hourly. Moderate to severe pain: IM/SC: 5-20 mg;

Intravenous: 2.5-10 mg via slow inj over 4-5 min or a starting dose of 1-2 mg/hr via continuous infusion (max: 100 mg/day; 4 g/day in cancer patients).

**CONTRAINDICATIONS**

Acute hepatic disease, obstructive airway disease, respiratory depression, delayed gastric emptying, paralytic ileus, morphine sensitivity.

**DRUG INTERACTIONS**

↓ dose with CNS depressants, muscle relaxants, MAOIs. With cimetidine, confusion and respiratory depression may occur. Morphine antagonizes efficacy of diuretics. Analgesia with NSAIDs.

**ADVERSE EFFECTS**

Nausea, vomiting, tolerance, constipation, dependence, urinary retention.

**SPECIAL PRECAUTIONS**

Use cautiously in hypothyroidism, renal/chronic hepatic disease. Dose reduction needed in elderly as respiratory depression may occur with increased frequency.

**OXYCODONE**

Opioid therapy

**INDICATION**

Moderate to severe pain.

**MECHANISM OF ACTION**

It stimulates receptors on nerves in the brain to increase the threshold to pain (increasing the amount of stimulation it takes to feel pain) and reduce the perception of pain (the perceived importance of the pain).

**DOSAGE**

Adult: Oral initially, 5 mg 4-6 hrly may increase as necessary; extended-release tab: 5-10 mg 12 hrly. Max: 400 mg/day; IV as inj: 1-10 mg over 1-2 min, repeated not more often than 4 hrly; as infusion: Initial: 2 mg/hr, increased as necessary. Patient-controlled analgesia (PCA): 0.03 mg/kg, admin w/ a minimum lock-out time of 5 min; SC As inj: Initial: 5 mg 4 hrly. As infusion: Initial: 7.5 mg/day adjusted according to response.

**CONTRAINDICATIONS**

Respiratory depression, known or suspected paralytic ileus, acute abdomen, delayed gastric emptying, COPD, cor pulmonale, acute or chronic bronchial asthma, hypercarbia, chronic constipation. Concurrent administration of MAOIs or w/in 2 week of discontinuation of use. Moderate to severe hepatic and severe renal impairment. Lactation.

**DRUG INTERACTIONS**

Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with oxycodone because they may reduce analgesic effect of oxycodone or precipitate withdrawal symptoms

**ADVERSE EFFECTS**

Nausea, constipation, vomiting, respiratory depression, headache, pruritus, insomnia, dizziness, asthenia, somnolence, abdominal

pain, chills and fever, hypotension, anorexia, diarrhea, dyspepsia, dysphagia, anxiety, nervousness, tremor, vasodilation, cough, dyspnea, rash.

**SPECIAL PRECAUTION**

Patient with raised intracranial pressure, hypotension, hypovolemia, toxic psychosis, biliary tract diseases, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, history of drug abuse or acute alcoholism, delirium, thyroid dysfunction. Mild to moderate renal and mild hepatic impairment. Pregnancy. Patient counselling may impair ability to drive or operate machinery. Monitoring parameters: Monitor pain relief, resp and mental status, BP; signs of misuse, abuse, and addiction; signs or symptoms of hypogonadism or hypoadrenalism.

**TRAMADOL**

Opioid therapy

**INDICATIONS**

Moderate to severe and acute or chronic pain, painful diagnostic procedures and surgical pain.

**MECHANISM OF ACTION**

it is a weak agonist at opioid receptors especially  $\mu$  receptors.

**DOSAGE**

Oral: Adults: 50-100 mg. BD/TID. Max.: 400 mg/day. Inj.: 100 mg IM/ SC or IV (slow infusion) per dose. Max.: 400 mg/day; Children 1-1.5 mg/kg.

**CONTRAINDICATIONS**

Hypersensitivity, acute CNS intoxication due to alcohol, analgesics and psychotropics,

respiratory depression, acute attack of asthma, raised intracranial pressure or head injury.

**DRUG INTERACTIONS**

$\uparrow$  sedation with tranquilizers, hypnotics MAOIs cause fatal interaction. Opioid analgesics like buprenorphine, pentazocine precipitate withdrawal symptoms.

**ADVERSE EFFECTS**

Nausea, vomiting, dizziness, sweating, stupor, hypotension/hypertension, anaphylaxis and psychiatric reactions.

**SPECIAL PRECAUTIONS**

Use cautiously in inflammatory and obstructive bowel disease,

myasthenia gravis, adrenocortical insufficiency. Reduce dose in hepatic or renal disease, epilepsy, pregnancy. Avoid driving and operating heavy machinery. During pregnancy and lactation use only if potential benefits outweigh the potential risks.

**Durogesic<sup>®</sup>**

fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC<sup>™</sup>**

Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET<sup>®</sup>**

(Tramadol 37.5 mg + Paracetamol 325 mg)

## ► MISCELLANEOUS DRUGS &gt; mTOR INHIBITOR

TEMSIROLIMUS		mTOR Inhibitor
<b>INDICATION</b> Advanced renal cell carcinoma.	<b>CONTRAINdications</b> Not to be used in patients with bilirubin $>1.5 \times$ upper limit of normal.	<b>SPECIAL PRECAUTIONS</b> Hypersensitivity reactions have been reported, use with caution in patients with hepatic impairment. Hyperglycemia may occur. Bowel perforation may occur.
<b>MECHANISM OF ACTION</b> Stimulates protein synthesis by phosphorylating translation regulators, and contributes to protein degradation and angiogenesis	<b>DRUG INTERACTIONS</b> Strong inducers of CYP3A4/5 and inhibitors of CYP3A4 may affect concentrations of the primary metabolite of the drug.	
<b>DOSAGE</b> 25 mg infusion over a 30- 60 minute period once a week.	<b>ADVERSE EFFECTS</b> Rash, asthenia, mucositis, nausea, edema, and anorexia.	

## ► MISCELLANEOUS DRUGS &gt; IMMUNE THERAPIES

ALDESLEUKIN		Immune therapy
<b>INDICATION</b> Metastatic renal cell carcinoma and melanoma.	<b>CONTRAINDICATIONS</b> thallium stress test, with organ allograft, chest pain, sustained ventricular tachycardia, angina, myocardial infarction, cardiac tamponade, renal failure requiring dialysis and abnormal pulmonary function. Cardiac arrhythmias not controlled on treatment. Patients intubated for more than 72 hours, coma or toxic psychosis for more than 48 hours. Repeated seizures. Bowel ischemia/perforation and GI bleeding requiring surgery	<b>SPECIAL PRECAUTIONS</b> Reduced kidney and liver function subsequent to treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs. Hypersensitivity reactions reported in patients receiving combination regimens containing sequential high dose antineoplastic agents
<b>MECHANISM OF ACTION</b> Promotes B-cell and T-cell proliferation and induces cytokine cascade to attack the tumor	<b>DRUG INTERACTIONS</b> Interactions may occur following concomitant administration of psychotropic drugs including narcotics, analgesics, antiemetics, sedatives, tranquilizers. Interactions with concurrent administration of drugs possessing nephrotoxic such as aminoglycosides, indometacin; myelotoxic drugs, cardiotoxic agents and hepatotoxic drugs.	<b>ADVERSE EFFECTS</b> Hypotension, red and itching skin, liver and kidney function test changes, fluid and electrolyte imbalance, high fever, injection site reactions.
<b>DOSAGE</b> Adults: Metastatic renal cell carcinoma or metastatic melanoma: Induction dose: 18 million u/m <sup>2</sup> /24 hr via continuous infusion for 5 days, and 2-6 days of rest, followed by another 5 days of infusion, and rest for 3 week. Start 2 <sup>nd</sup> cycle after the 3-week rest period. A total of 4 maintenance cycles may be administered at an interval of 4 weeks to responders or patients whose disease stabilizes.		<b>SPECIAL PRECAUTIONS</b> May cause drug-induced shock like state, use to be limited to patients with normal cardiac and pulmonary functions.
<b>CONTRAINDICATIONS</b> Known hypersensitivity to ingredients. Patients with abnormal		

**INTERFERON**

Immune therapy

**INDICATIONS**

Hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic granulocytic leukemia, recurrent or metastatic renal cell carcinoma, chronic active hepatitis B and C, progressive cutaneous T-cell lymphoma.

**MECHANISM OF ACTION**

It inhibits replication of RNA and DNA viruses along with antiproliferative effects on normal and malignant cells. It also suppresses antibody formation through an effect on B-lymphocytes.

**DOSAGE**

Adults: The dosage is calculated taking into account the body

surface area and the condition being treated.

**CONTRAINDICATION**

Hypersensitivity.

**DRUG INTERACTIONS**

A number of drugs increase the risk of adverse effects on the blood, heart or nervous system. This is taken into account when prescribing an interferon with other drugs. Theophylline effects on concomitant use. Sedatives (anxiolytics, hypnotics, antihistamines, antidepressants, narcotic analgesics and antipsychotics) have added sedative effects on the nervous system on concomitant use.

**ADVERSE EFFECTS**

Headache, lethargy/depression, dizziness/drowsiness, digestive disturbances, fever/chills, hair loss.

**SPECIAL PRECAUTIONS**

Use cautiously in chronic hepatic or renal disorder, heart disease, epilepsy, previous allergic reactions to any drugs, asthma or eczema, depression and with other medications. Reduced doses may be necessary. Increased likelihood of adverse effects in elderly. Safety in pregnancy not established. It is not known whether the drug passes into breastmilk. Alcohol may increase the sedative effects of this drug.

## ► MISCELLANEOUS DRUGS &gt; HORMONAL THERAPIES

**FLUTAMIDE**

Hormonal therapy

**INDICATIONS**

Advanced prostatic carcinoma.

**MECHANISM OF ACTION**

Direct action on the target tissues either by blocking androgen uptake or by inhibiting cytoplasmic and nuclear binding of androgen.

**DOSAGE**

Adults: Oral: 250 mg TID/day.

**CONTRAINDICATIONS**

Hypersensitivity.

**DRUG INTERACTIONS**

Warfarin causes ↑ prothrombin time.

**ADVERSE EFFECTS**

GI upsets, gynecomastia, hemolytic anemia, methemoglobinemia, hot flushes, impotence, loss of libido.

**SPECIAL PRECAUTION**

Use cautiously in G6PD deficiency and in increased risk of adverse effects in elderly. Monitor liver function periodically. It may cause fetal harm. Alcohol leads to increased adverse effects.

**GOSERELIN**

Hormonal therapy

**INDICATIONS**

Palliation of prostatic carcinoma.

**MECHANISM OF ACTION**

It inhibits pituitary gonadotropin secretion. In males, it increases serum LH, FSH and testosterone levels. In females, a similar down-regulation of the pituitary gland leads to suppression of gonadotropin secretion, a decrease in serum estradiol to levels consistent with the postmenopausal state, and this leads to a reduction of ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone responsive tumors, if present.

**DOSAGE**

Adult: Subcutaneous 6 mg, administer every 28 days into the upper abdominal wall. While a delay of a few days is permissible, every effort should be made to adhere to the 28-day schedule. Treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy, 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by 10.8 mg depot. Alternatively, four inj of 3.6 mg depot administered at 28 days interval, two depots preceding and two during radiotherapy.

**CONTRAINDICATION**

Hypersensitivity, pregnancy, lactation.

**ADVERSE EFFECTS**

Urticaria, hot flashes, sexual dysfunction, decreased erections, lower urinary tract infection (LUTI) symptoms, lethargy, pain (worsened in the first 30 days), edema, urticaria.

**SPECIAL PRECAUTIONS**

Care should be taken when dilating the cervix for endometrial ablation. Non-hormonal method of contraception should be used during treatment.

**Durogesic®**

fentanyl transdermal system

12 mcg/hr, 25 mcg/hr, 50 mcg/hr

**PRELOGIC™**

Pregabalin 75mg + Methylcobalamin 750mcg

**ULTRACET®**

(Tramadol 37.5 mg + Paracetamol 325 mg)



LEUPRORELIN		Hormonal therapy
<b>INDICATIONS</b> Advanced prostatic cancer, anemia caused by bleeding of uterine leiomyomas (tumors in the uterus), pain due to endometriosis in women.	<b>CONTRAINDICATIONS</b> Pregnancy, lactation and hypersensitivity.	<b>SPECIAL PRECAUTIONS</b> Flare phenomenon to reduce risk of flare on initial therapy, an anti-androgen may be administered 3 days before therapy and continued for 2-3 weeks. Patients at risk of ureteric obstruction, metastatic vertebral lesions and spinal cord compression; monitor in first few weeks and consider anti-androgens.
<b>MECHANISM OF ACTION</b> It is a luteinizing hormone-releasing hormone (LH-RH) agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses.	<b>DRUG INTERACTIONS</b> Note specified.	
<b>DOSAGE</b> Adults: 1 mg/day as single SC injection. Vary injection site daily.	<b>ADVERSE EFFECTS</b> Paresthesia, hot flushes, hyperglycemia. Transient increase in bone pain and urinary obstruction. Impotence, decreased libido. Rarely, peripheral edema, fatigue, nausea, irritation at injection site.	

## ► MISCELLANEOUS DRUGS > OTHER HORMONAL THERAPIES

ANASTROZOLE		Other hormonal therapy
<b>INDICATIONS</b> Advanced breast cancer in postmenopausal women.	<b>CONTRAINDICATIONS</b> Pregnancy; premenopausal women.	<b>SPECIAL PRECAUTIONS</b> Fractures, rash (including Stevens-Johnson syndrome). Asthenia and drowsiness may initially affect ability to drive or operate machinery.
<b>MECHANISM OF ACTION</b> Anastrozole is a new generation nonsteroidal aromatase inhibitor, which selectively and potently blocks the enzymatic synthesis of estrogen from androgen.	<b>DRUG INTERACTION</b> Estrogen containing therapies should not be used with anastrozole; tamoxifen should not be coadministered with anastrozole.	<b>ADVERSE EFFECTS</b> Hot flushes, vaginal dryness, vaginal bleeding, hair thinning, anorexia, nausea, vomiting, diarrhea, headache, arthralgia, bone
<b>DOSAGE</b> 1 mg daily.		

EXEMESTANE		Other hormonal therapy
<b>INDICATION</b> Advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.	<b>CONTRAINDICATIONS</b> Hypersensitivity. Premenopausal women. Pregnancy and lactation.	<b>SPECIAL PRECAUTIONS</b> Peripheral edema, constipation, dyspepsia.
<b>MECHANISM OF ACTION</b> Reversible aromatase inhibitor that bind to the aromatase enzyme and block the production of estrogen from androgens.	<b>DRUG INTERACTIONS</b> CYP3A4 inducers may significantly decrease exposure to exemestane	<b>ADVERSE EFFECTS</b> Hot flushes, nausea, fatigue, increased sweating, headache, dizziness, insomnia, skin rash, abdominal pain, anorexia, vomiting, dyspepsia, depression, alopecia,
<b>DOSAGE</b> Oral: 25 mg tablet once daily after a meal.		

► MISCELLANEOUS DRUGS > OTHER AGENTS

HYDROXYUREA	!	Other agent
<b>INDICATIONS</b> Chronic granulocytic leukemia, Non-Hodgkin's lymphoma, polycythemia vera, thrombocythemia, solid malignancies (with radiotherapy); Gestational trophoblastic tumors, carcinoma head and neck, cervix, ovary.	3 days x indefinitely (if benefit apparent after 6 weeks).	drowsiness, disorientation, hallucination, seizures, hepatitis, and flu-like syndrome.
<b>MECHANISM OF ACTION</b> It blocks conversion of ribonucleotides to deoxyribonucleotides by inhibiting the enzyme ribonucleotide reductase interfering with DNA synthesis.	<b>CONTRAINDICATIONS</b> Severe marrow suppression.	<b>SPECIAL PRECAUTIONS</b> Use cautiously in renal impairment, hepatic disease and concurrent medication. Hb, TLC, platelets and hepatic/renal parameters should be monitored during Rx. Stop Rx if TLC <2,500 or platelets <1,00,000 mm <sup>3</sup> . The patient's urine should be handled with protective clothing for upto 48 hrs after the last drug dose. Stop Rx in the case of a fracture. Caution in reduced renal functional status.
<b>DOSAGE</b> <i>Malignancies:</i> Oral 20-30 mg/kg OD or 80 mg/kg (single dose) every	<b>DRUG INTERACTIONS</b> Cytarabine: Hematological untoward effects. CNS depressants: CNS depression. Live attenuated vaccines: The vaccine may prove virulent. Radiotherapy: erythema.	<b>ADVERSE EFFECTS</b> Marrow suppression, especially megaloblastic changes; GI disturbances, pulmonary edema, skin reactions, alopecia, renal dysfunction, headache, dizziness,

THALIDOMIDE	!  x	Other agent
<b>INDICATIONS</b> Multiple myeloma and Kaposi's sarcoma.	<b>CONTRAINDICATIONS</b> Contraindicated in pregnant women. The drug should not be initiated in patients with absolute neutrophil counts (ANC) less than 750/mm <sup>3</sup> . Hypersensitivity to the drug or any ingredient in the formulation.	hypotension, murmur, myocardial infarction, palpitation, pericarditis, peripheral vascular disorder, postural (orthostatic) hypotension, syncope, tachycardia, thrombophlebitis, thrombosis, and vasodilation.
<b>MECHANISM OF ACTION</b> Thalidomide possesses immunomodulatory, anti-inflammatory and antiangiogenic properties. The immunomodulatory and anti-inflammatory effects of thalidomide appear to result from modulation of tumor necrosis factor alpha (TNF-α) levels, co-stimulatory or adjuvant effect on T-cells resulting in increased T-cell proliferation and increased production of interleukin-2 and interferon-γ, and/or modulation of leukocyte migration and chemotaxis. Thalidomide inhibits angiogenesis, and it has been suggested that the teratogenic effects of thalidomide on fetal limbs may be related to inhibition of blood vessel growth in the developing fetal limb bud.	<b>DRUG INTERACTIONS</b> Enhances the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.	<b>SPECIAL PRECAUTIONS</b> Male patients receiving thalidomide should be instructed to inform their clinician if they have unprotected heterosexual sexual contact while receiving thalidomide. All women and adolescent females of childbearing potential and all sexually mature males receiving thalidomide must use effective contraceptive measures to help ensure that fetal exposure to thalidomide does not occur. Patients should be instructed to immediately report initial symptoms (e.g., numbness, tingling, pain or a burning sensation in the hands and feet) of peripheral neuropathy. Because thalidomide may cause dizziness and orthostatic hypotension, patients receiving the drug should be instructed to sit upright for a few minutes before standing up from a reclining position.
<b>DOSAGE</b> <i>Multiple myeloma:</i> Administered in combination with dexamethasone in 28-day treatment cycles, 200 mg once daily. Maximum dose: 800 mg/day.	<b>ADVERSE EFFECTS</b> Drowsiness/somnolence, peripheral neuropathy, dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase, constipation, hypocalcemia, edema, dyspnea, thrombosis/embolism, and rash/desquamation, apnea, bronchitis, cough, emphysema, epistaxis, lung disorder, lung edema, pneumonia (including that caused by <i>Pneumocystis carinii</i> ), pulmonary embolus, upper respiratory infection, and voice alteration, angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral ischemia, cerebrovascular accident, chest pain, congestive heart failure, deep thrombophlebitis, heart arrest, heart failure, hypertension,	



**LENALIDOMIDE**

Other agents

**INDICATIONS**

Transfusion-dependent anemia due to low- or intermediate-risk myelodysplastic syndromes, multiple myeloma (in combination with dexamethasone).

**MECHANISM OF ACTION**

Lenalidomide, a thalidomide analog, is an immunomodulatory agent with antineoplastic and antiangiogenic activity. Lenalidomide inhibits the secretion of pro-inflammatory cytokines and increased the secretion of antiinflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibits the growth of multiple myeloma cells from patients, as well as MM.1S cells (a human multiple myeloma cell line), by inducing cell cycle arrest and apoptosis.

**DOSAGE**

*Myelodysplastic syndrome:* 10 mg once daily. *Multiple myeloma:* 25 mg once daily (as a single 25-mg capsule) on days 1–21 of repeated 28-day cycles. Patients

also should receive an oral 40-mg dexamethasone dose once daily on days 1–4, 9–12, and 17–20 of each 28-day cycle for the first 4 cycles of therapy, followed by an oral 40-mg dexamethasone dose once daily on days 1–4 of each subsequent 28-day cycle.

**CONTRAINDICATIONS**

Contraindicated in women who are pregnant and in females of childbearing potential, known hypersensitivity to the drug or any ingredient in the formulation.

**DRUG INTERACTIONS**

Potential pharmacokinetic interaction with digoxin (increased peak plasma digoxin concentration).

**ADVERSE EFFECTS**

MDS: Thrombocytopenia, neutropenia, diarrhea, pruritus, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, back pain, fever, peripheral edema, cough, dizziness, headache, muscle cramps, dyspnea, pharyngitis, asthenia, epistaxis, upper respiratory tract

infection, dry skin, abdominal pain, anemia, pneumonia, hypokalemia, limb pain, urinary tract infection, anorexia, edema, insomnia, and vomiting.

Multiple myeloma: Constipation, fatigue, insomnia, muscle cramps, diarrhea, neutropenia, anemia, asthenia, fever, nausea, headache, peripheral edema, dizziness, dyspnea, tremor, weight loss, thrombocytopenia, rash, back pain, hyperglycemia, muscle weakness, blurred vision, cough, dyspepsia, anorexia, upper respiratory tract infection, dysgeusia, paresthesia, hypokalemia, pneumonia, arthralgia, and vomiting.

**SPECIAL PRECAUTIONS**

Patients with a prior history of grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Patients should be monitored for signs and symptoms of thromboembolism. Careful dosage selection and monitoring of renal function are advised in geriatric patients.

► MISCELLANEOUS DRUGS > COMBINATION THERAPY

**TRAMADOL + PARACETAMOL**

Combination therapy

**INDICATION**

Moderate to severe pain.

**MECHANISM OF ACTION**

Tramadol binds to mu-opioid receptors and weakly inhibits the reuptake of norepinephrine and serotonin. Paracetamol is a para-aminophenol derivative with analgesic, antipyretic and weak anti-inflammatory action. The combination of tramadol and paracetamol has a rapid onset of action compared to tramadol alone and longer duration of action compared to paracetamol alone. It is absorbed from the gastrointestinal tract.

**DOSAGE**

Oral (Adults): *For moderate to severe pain:* Each tablet consists of tramadol HCl 37.5 mg and paracetamol 325 mg, 2 tablets

6 hourly. Up to a maximum of 8 tablets per day, maximum 5 days.

**CONTRAINDICATIONS**

Severe hepatic impairment, acute intoxication to hypnotics, centrally-acting analgesics, opioids, alcohol. Severe hepatic impairment. Coadministration with MAOIs or within 2 weeks after withdrawal of MAOIs.

**DRUG INTERACTIONS**

Increases the risk of seizures, and serotonin syndrome with Coadministration of SSRIs, SNRIs, TCAs, and 5-HT agonists. Increases the risk of CNS depression with barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.

Analgesic efficacy decreased with ondansetron.

**ADVERSE EFFECTS**

Respiratory depression, postural hypertension, Stevens-Johnson syndrome, bradycardia, collapse, allergic reactions, motor weakness, mood alleviation, cognitive changes, changes in sensorial capacity, skin rash, and blood dyscrasias.

**SPECIAL PRECAUTIONS**

Use cautiously in patients with epilepsy, risk of seizures, biliary tract disorder, altered consciousness, impaired respiratory function, increased intracranial pressure, suicidal tendency. May cause dependence and withdrawal symptoms, and compromised motor skills.

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Additional information available on request

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