SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIAQUI-DF® Paracetamol 325 mg, Diclofenac Sodium 50 mg, and Caffeine 30 mg Effervescent Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each effervescent tablet contains:

- **Paracetamol** (Acetaminophen, BP grade)
- **Diclofenac Sodium** (NSAID, BP grade)
- **Caffeine** (BP grade)

2.2 Quantitative Declaration

Active Ingredient	Strength	Pharmacopeial Standard
Paracetamol	325 mg	BP/USP
Diclofenac Sodium	50 mg	BP/USP
Caffeine	30 mg	BP/USP

For a full list of excipients, see section 6.1.

2.3 Pharmaceutical Form and Appearance

Pharmaceutical Form: Effervescent Tablet

Appearance Description: Round, white to off-white effervescent tablets with smooth surface and slight orange fragrance. The tablet measures approximately 19 mm in diameter and 8 mm in thickness (approximate weight 4.5 grams per tablet). The tablets are embossed with "TRIAQUI-DF 50" on one side and plain on the reverse.

pH of aqueous solution (1% in water at 25°C): 3.0-3.5

Osmolarity: Hypertonic (approximately 400 mOsm/kg)

3. PHARMACEUTICAL FORM

Effervescent tablets are white to off-white, round, flat-faced tablets with beveled edges. Upon dissolution in water, the tablets release carbon dioxide gas producing an effervescent solution with a characteristic effervescent action and pleasant taste. The tablets should be dissolved in approximately 100-150 mL of water before administration.

The effervescent form allows for:

- Rapid dissolution and enhanced bioavailability
- Faster onset of action compared to conventional tablets
- Improved palatability
- Better absorption due to increased surface area

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

TRIAQUI-DF® is indicated for:

Acute mild to moderate pain including headache, dental pain, and myalgia

Fever management in adults and adolescents above 15 years of age

Symptomatic treatment of pain and inflammation associated with:

Musculoskeletal pain and strain

Dysmenorrhea (menstrual pain)

Rheumatic disorders

Post-operative pain

Headache and migraine (adjunctive therapy)

Musculoskeletal disorders with inflammatory components

Minor injuries and sprains with associated pain and swelling

The combination of paracetamol and diclofenac sodium provides synergistic analgesic and anti-inflammatory action, while caffeine enhances pain relief and alertness, making this product particularly effective for conditions requiring combined analgesic and anti-inflammatory therapy.

4.2 Posology and Method of Administration

Dosage for Adults (18 years and above):

Standard dose: One effervescent tablet (Paracetamol 325 mg + Diclofenac Sodium 50 mg + Caffeine 30 mg) dissolved in water

Frequency: Every 6-8 hours as required for pain relief

Maximum daily dose: Three tablets in 24 hours (not to exceed 975 mg Paracetamol and 150 mg Diclofenac Sodium daily)

Duration: Should not be used continuously for more than 7 days without medical consultation

Dosage for Elderly Patients (65 years and above):

Elderly patients should receive the same dose as adults; however, careful consideration should be given to renal and hepatic function:

Maximum daily dose should not exceed 2 tablets in 24 hours

Baseline assessment of renal function (eGFR) recommended before treatment initiation

Close monitoring for gastrointestinal side effects is essential

Dosage for Adolescents (15-17 years):

Dose: One tablet every 6-8 hours as required

Maximum daily dose: Not to exceed 2 tablets in 24 hours (650 mg Paracetamol + 100 mg Diclofenac Sodium)

Duration: Short-term use only (maximum 3 days without medical review)

Children (under 15 years):

TRIAQUI-DF® is NOT recommended for children under 15 years of age. Use in pediatric populations requires careful benefit-risk assessment and is contraindicated in most cases due to the combination of active ingredients.

Method of Administration:

Dissolve one tablet in approximately 100-150 mL of fresh water at room temperature or warm water

Stir well for approximately 30-60 seconds until the tablet is completely dissolved

Drink the entire solution immediately after dissolution

Do not swallow the tablet whole

To improve taste, the solution may be consumed with a small amount of fruit juice or lemon juice if desired

No food restriction; may be taken with or without food, though taking with a light meal may reduce gastrointestinal irritation

4.3 Contraindications

TRIAQUI-DF® is contraindicated in patients with:

Hypersensitivity to paracetamol, diclofenac sodium, caffeine, or any component of the formulation

Known cross-reactivity to other NSAIDs (e.g., aspirin, ibuprofen, indomethacin, naproxen)

History of allergic reactions manifesting as:

Bronchospasm

Anaphylactic reactions

Urticaria or rash

Angioedema

Rhinitis following NSAID use

Active gastric and/or duodenal ulceration or history of peptic ulcer disease within the past 12 months

Gastrointestinal bleeding or history of GI bleeding within the past 12 months

Inflammatory bowel disease including Crohn's disease or ulcerative colitis (high risk of exacerbation and severe complications)

Severe hepatic impairment (Child-Pugh Class C or AST/ALT >3 times upper limit of normal)

Severe renal impairment (eGFR <30 mL/min/1.73m²)

Severe cardiac failure (NYHA Class III or IV)

Recent myocardial infarction (within 6 months)

Coronary artery disease or stroke risk

Third trimester of pregnancy

Breastfeeding (diclofenac and caffeine pass into breast milk)

Porphyria cutanea tarda (risk of acute porphyric crisis)

Uncontrolled hypertension (systolic BP >180 mmHg and/or diastolic BP >110 mmHg)

4.4 Special Warnings and Precautions for Use

Cardiovascular Warnings:

NSAIDs, including diclofenac, are associated with an increased risk of thrombotic cardiovascular events (myocardial infarction and stroke), particularly in elderly patients and those with established cardiovascular disease

Use with extreme caution in patients with cardiovascular disease, hypertension, or significant cardiovascular risk factors

Patients should be monitored for signs and symptoms of cardiovascular events

Gastrointestinal Warnings:

NSAIDs increase the risk of serious gastrointestinal complications including bleeding, ulceration, and perforation

The risk is higher in:

Patients aged >65 years

Patients with history of peptic ulcer disease

Patients on concurrent corticosteroid or anticoagulant therapy

Patients with H. pylori infection

Long-term use of NSAIDs is associated with gastric ulceration in 15-20% of patients

Gastroprotection with a proton pump inhibitor (e.g., omeprazole 20 mg daily) should be considered in high-risk patients

Hepatic Impairment:

Use with caution in patients with mild to moderate hepatic impairment

Baseline liver function tests (ALT, AST, bilirubin) are recommended

Paracetamol is hepatotoxic at high doses, particularly in patients with pre-existing liver disease or chronic alcohol consumption

Patients with hepatic impairment should not exceed 2 tablets in 48 hours

Renal Impairment:

NSAIDs can impair renal function, particularly in patients with pre-existing renal disease

Baseline serum creatinine and eGFR assessment is recommended

Caution in patients with eGFR 30-60 mL/min; avoid if eGFR <30 mL/min

Patients on chronic diuretic therapy may have increased risk of acute kidney injury

Hematologic Precautions:

NSAIDs impair platelet function and may increase bleeding risk

Use with caution in patients on anticoagulants (warfarin, DOACs) or antiplatelet agents (aspirin, clopidogrel)

Baseline complete blood count recommended for long-term use

Drug Interaction Warnings:

Do not combine with other NSAIDs, aspirin, or COX-2 inhibitors

Caffeine content may cause jitteriness when combined with other stimulants (e.g., decongestants, weight-loss products)

Risk of serotonin syndrome when used with SSRIs or SNRIs

May reduce effectiveness of antihypertensive medications

Increased GI bleeding risk with concurrent corticosteroids or anticoagulants

Caffeine-Related Precautions:

Total daily caffeine intake from all sources should be monitored (recommended maximum: 400 mg/day from all sources)

Patients with caffeine sensitivity should be identified

Anxiety, insomnia, tremor, and palpitations may occur, particularly in susceptible individuals

Not recommended for patients with cardiac arrhythmias or uncontrolled hypertension

Pregnancy and Lactation:

Second trimester: May be used with caution for short periods only

Third trimester: Absolutely contraindicated (risk of delayed delivery, IUGR, ductus arteriosus closure)

Breastfeeding: Contraindicated; active metabolites pass into breast milk and may accumulate in the infant

Paracetamol is preferred analgesic during pregnancy; NSAIDs should be avoided

Special Populations:

Elderly patients: Increased sensitivity to NSAIDs; require lower doses and more frequent monitoring

Asthma: NSAIDs may precipitate bronchospasm in patients with aspirin sensitivity

Glucose-6-phosphate dehydrogenase (G6PD) deficiency: Paracetamol may cause hemolysis

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Major Drug Interactions:

Drug Class	Specific Drug	Mechanism	Clinical Significance
NSAIDs/Salicylates	Ibuprofen, aspirin, naproxen	Additive GI toxicity	Severe GI bleeding risk; AVOID
Anticoagulants	Warfarin, DOAC (apixaban, rivaroxaban)	Impaired platelet function	Increased bleeding risk
Antiplatelet agents	Aspirin, clopidogrel, ticlopidine	Additive antiplatelet effect	Increased bleeding risk

ACE Inhibitors	Enalapril, lisinopril, ramipril	Reduced antihypertensive effect	Blood pressure control loss
Angiotensin II Receptor Blockers	Losartan, valsartan, irbesartan	Reduced antihypertensive effect; acute renal failure risk	Monitor BP and renal function
Beta-blockers	Metoprolol, atenolol, propranolol	Reduced antihypertensive effect	Decreased efficacy
Diuretics	Furosemide, hydrochlorothiazide, spironolactone	Reduced diuretic and antihypertensive effect; hyperkalemia risk	Acute kidney injury risk
Corticosteroids	Prednisolone, dexamethasone, methylprednisolone	Additive GI ulceration risk	Severe GI bleeding
Methotrexate	Methotrexate (low-dose)	Reduced renal clearance of methotrexate	Methotrexate toxicity
Lithium	Lithium carbonate	Reduced renal clearance of lithium	Lithium toxicity; tremor, confusion
SSRIs/SNRIs	Fluoxetine, sertraline, venlafaxine, duloxetine	CNS serotonin accumulation	Serotonin syndrome risk
Stimulants	Pseudoephedrine, phentermine, methylphenidate	Additive sympathomimetic effects	Tachycardia, hypertension, anxiety
Alcohol	Ethanol	Hepatotoxicity risk (paracetamol); GI irritation (NSAID)	Severe hepatotoxicity, GI bleed
Probenecid	Probenecid	Reduced diclofenac elimination	Increased diclofenac levels

Moderate Drug Interactions:

- **H2-receptor antagonists (cimetidine, ranitidine):** May reduce NSAID efficacy
- **Oral hypoglycemics:** NSAIDs may enhance hypoglycemic effect; monitor blood glucose
- **Tacrolimus:** Increased risk of renal impairment
- **Cyclosporine:** Increased risk of nephrotoxicity

Food and Caffeine Interactions:

- **Excessive caffeine sources:** Coffee (95 mg/cup), tea (25-50 mg/cup), cola beverages (35-45 mg/can), dark chocolate (10-30 mg/serving)
- Combined intake may cause jitteriness, palpitations, insomnia, and anxiety
- **Alcohol:** Should be avoided due to increased hepatotoxicity and GI bleeding risk

4.6 Fertility, Pregnancy and Lactation

Pregnancy:

First Trimester:

- Paracetamol is considered safe; NSAIDs are generally avoided
- TRIAQUI-DF is not recommended due to diclofenac and caffeine content
- If acetaminophen monotherapy is required, paracetamol alone should be used

Second Trimester:

- Use only if essential and for short periods (no more than 3-5 days)
- Risk-benefit assessment must be performed by physician
- Diclofenac: Risk of fetal renal dysfunction and oligohydramnios
- Caffeine: Some evidence of increased miscarriage risk at high doses (>200 mg/day)

Third Trimester (Contraindicated):

- Absolutely contraindicated
- High risk of:
    - Premature ductus arteriosus closure
    - Oligohydramnios
    - Intrauterine growth restriction
    - Delayed delivery
    - Increased perinatal mortality

Lactation:

- **Contraindicated during breastfeeding**
- Paracetamol: 0.04-0.23% of maternal dose excreted in breast milk; minimal risk

- Diclofenac: 0.01% excreted in breast milk; minimal direct risk but NSAID accumulation possible
- Caffeine: 0.06-1.5% excreted in breast milk; can accumulate in neonates causing irritability and sleep disturbances
- **Recommendation:** Breastfeeding mothers should use paracetamol monotherapy or alternative agents

Fertility:

- NSAIDs may impair female fertility by interfering with ovulation (reversible)
- Chronic use may affect male fertility through effects on testicular function (reversible)
- Effects are typically reversible upon discontinuation

4.7 Effects on Ability to Drive and Use Machines

TRIAQUI-DF® may impair driving ability and alertness in some patients due to:

1. Caffeine-induced jitteriness, anxiety, or insomnia (in sensitive individuals)
2. Headache or dizziness from rapid diclofenac absorption
3. Potential CNS effects from paracetamol-related fever reduction affecting judgment

Recommendations:

- Patients should avoid driving or operating machinery if experiencing dizziness, drowsiness, or impaired concentration
- Initial response to medication should be assessed before driving
- Use caution, particularly on first dose or when increasing frequency

4.8 Undesirable Effects (Adverse Drug Reactions)

Frequency Classification:

Frequency	Definition
Very common	≥1/10 (≥10%)
Common	≥1/100 to <1/10 (1-10%)
Uncommon	≥1/1,000 to <1/100 (0.1-1%)
Rare	≥1/10,000 to <1/1,000 (0.01-0.1%)
Very rare	<1/10,000 (<0.01%)

Adverse Effects by System:

Gastrointestinal Disorders (Very Common - Common):

- Dyspepsia and heartburn (2-8%)
- Abdominal pain and cramping (1-3%)
- Nausea (1-2%)
- Diarrhea (1-2%)
- Constipation (0.5-1%)
- Peptic ulcer with bleeding (0.5-1% with chronic use)
- Gastroesophageal reflux disease (1%)

Central Nervous System (Common - Uncommon):

- Headache (2-3%, often rebound headache with prolonged use)
- Dizziness and lightheadedness (1-2%)
- Tremor and jitteriness (1%, caffeine-related)
- Insomnia and sleep disturbance (0.5-1%, caffeine-related)
- Anxiety and nervousness (0.5-1%, caffeine-related)
- Drowsiness (0.5%)

Cardiovascular (Uncommon - Rare):

- Palpitations and tachycardia (1%, caffeine-related)
- Hypertension (0.5-1%)
- Myocardial infarction (0.1-0.5% with chronic use, NSAID-related)
- Stroke (0.1-0.5% with chronic use, NSAID-related)
- Peripheral edema (0.5-1%)

Hepatic (Uncommon - Rare):

- Elevated liver enzymes (ALT, AST) (1-2%)
- Hepatotoxicity and acute liver failure (<0.01%, paracetamol-related, usually with overdose)
- Jaundice (rare)

Renal (Uncommon - Rare):

- Acute kidney injury (0.1-0.5%, NSAID-related)
- Elevated serum creatinine (0.5-1%)
- Proteinuria (0.1%)
- Acute interstitial nephritis (rare)

Hematologic (Rare - Very Rare):

- Thrombocytopenia (severe platelet count reduction) (<0.01%)
- Hemolytic anemia (rare)
- Agranulocytosis (<0.01%)

Dermatologic (Uncommon):

- Rash and urticaria (0.5-1%)
- Pruritus (0.5%)
- Stevens-Johnson Syndrome (very rare, <0.01%, paracetamol-related)
- Toxic epidermal necrolysis (very rare, <0.01%)

Hypersensitivity Reactions (Rare - Very Rare):

- Angioedema (0.1%)
- Anaphylaxis (<0.01%)
- Bronchospasm (0.1%, in aspirin-sensitive patients)

Ophthalmologic (Rare):

- Blurred vision (0.1%)
- Color blindness (very rare)

Metabolic/Endocrine (Uncommon):

- Hyperkalemia (elevated potassium, 0.5%, NSAID-related, particularly with renal impairment)
- Hyponatremia (low sodium, rare)

Musculoskeletal (Rare):

- Myalgia and muscle pain (0.1%)

Psychiatric (Uncommon):

- Anxiety and restlessness (0.5-1%, caffeine-related)
- Depression (0.1%)

Serious Adverse Effects Requiring Immediate Medical Attention:

1. **Severe GI bleeding** (coffee ground emesis, melena, severe abdominal pain)
2. **Signs of hepatotoxicity** (jaundice, dark urine, pale stools, severe nausea/vomiting)
3. **Signs of renal failure** (oliguria, anuria, edema, fatigue)
4. **Cardiovascular events** (chest pain, dyspnea, syncope, severe palpitations)
5. **Severe allergic reactions** (difficulty breathing, facial swelling, severe rash)
6. **Severe skin reactions** (widespread blistering, mucosal involvement)

4.9 Overdose

Clinical Features of Overdose:

Paracetamol Overdose (>140 mg/kg or >7 g in adults):

- Phase 1 (0-24 hours): Nausea, vomiting, anorexia, abdominal pain, profuse sweating
- Phase 2 (24-72 hours): False sense of recovery; right upper quadrant pain; elevation of liver enzymes (ALT, AST); hepatomegaly
- Phase 3 (>72 hours): Acute hepatic failure with jaundice, coagulopathy, encephalopathy, hypoglycemia, renal failure, death

Diclofenac Overdose (>300 mg):

- Nausea, vomiting, severe epigastric pain
- GI bleeding and perforation
- Acute renal failure
- Hypertension
- Cardiovascular collapse (in severe cases)

Caffeine Overdose (>1 g):

- Severe tremor, anxiety, agitation
- Tachycardia, palpitations, cardiac arrhythmias
- Hypertension

- Severe headache, insomnia, hallucinations
- Muscle fasciculations
- Seizures (in severe cases)

Management of Overdose:

Immediate Measures:

1. Discontinue the medication immediately
2. Seek emergency medical attention
3. Contact poison control center: (Emergency number in country of use)

Decontamination:

- If ingested within 4 hours: Gastric lavage or activated charcoal (50-100 g) may be considered
- Activated charcoal adsorbs paracetamol and NSAIDs; give 1 g/kg (maximum 50 g) within 1 hour of ingestion

Specific Treatment for Paracetamol Toxicity:

- **N-acetylcysteine (NAC):** Gold standard antidote
  - Loading dose: 150 mg/kg IV over 1 hour
  - Second infusion: 50 mg/kg IV over 4 hours
  - Third infusion: 100 mg/kg IV over 16 hours
  - Efficacy highest if started within 8 hours (but may help even if delayed)
- **Obtain baseline paracetamol level at 4+ hours post-ingestion and use Rumack-Matthew nomogram to determine risk**
- Monitor LFTs, PT/INR, serum creatinine, and blood glucose at baseline and regularly

Supportive Care:

- Maintain hydration; IV fluids as needed
- Monitor and manage electrolytes (particularly hyperkalemia)
- Hemodialysis: May be considered if renal function is severely impaired
- Monitor vital signs, ECG for arrhythmias
- Correct coagulopathy with Fresh Frozen Plasma (FFP) if PT/INR elevated
- Glucose supplementation if hypoglycemia develops
- Treat seizures with benzodiazepines if they occur

Monitoring:

- Repeat liver function tests daily until normalized
- Monitor renal function (creatinine, BUN)
- Coagulation profile (PT, INR, PTT)
- Blood glucose and arterial blood gases
- Continue NAC if INR elevated, hypoglycemia, or hepatic encephalopathy develops

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action:

Paracetamol (Acetaminophen):

- **Primary mechanism:** Inhibition of cyclooxygenase-1 (COX-1) and COX-2 enzymes in the central nervous system and peripheral tissues
- **Selectivity:** Preferentially inhibits COX-3 (a variant of COX-1) in the CNS
- **Effects:**
  - Analgesic: Raises the pain threshold by acting on the hypothalamic temperature-regulating center
  - Antipyretic: Reduces fever through action on the hypothalamus and prostaglandin E2 inhibition
  - Anti-inflammatory: Weak peripheral anti-inflammatory effect due to limited COX inhibition in peripheral tissues
- **Advantage over NSAIDs:** Minimal effect on platelet aggregation and GI mucosa, making it safer in many populations

Diclofenac Sodium (NSAID):

- **Primary mechanism:** Potent inhibition of COX-1 and COX-2 enzymes throughout the body
- **Potency:** More potent than paracetamol (approximately 2-3 times more potent as an analgesic)
- **Dual action:**
  - **Anti-inflammatory:** Inhibits prostaglandin synthesis, reducing prostaglandin E2 and I2, which mediate inflammation
  - **Analgesic:** Raises pain threshold and reduces pain perception through both peripheral and central mechanisms
  - **Antipyretic:** Reduces fever through hypothalamic action
- **Onset of action:** Rapid onset within 30-60 minutes (faster with salt form, diclofenac sodium)

- **Selectivity:** Slightly COX-1 selective at therapeutic doses, but inhibits both COX-1 and COX-2
- **Side effects:** More significant GI effects, cardiovascular effects, and renal effects compared to paracetamol due to widespread COX inhibition

Caffeine:

- **Primary mechanism:** Non-selective antagonism of adenosine receptors (particularly A1 and A2A receptors) in the CNS
- **Additional mechanisms:**
  - Inhibition of phosphodiesterase enzymes, increasing cAMP and cGMP
  - Release of catecholamines (epinephrine, norepinephrine)
- **CNS effects:** Stimulation of the reticular activating system, leading to increased alertness and reduced fatigue
- **Cardiovascular effects:** Mild increase in heart rate and blood pressure through sympathomimetic effects
- **Analgesic enhancement:** Caffeine potentiates analgesic effects of paracetamol and NSAIDs (approximately 40% increase in analgesic efficacy)
- **Mechanism of analgesic potentiation:** Increased CNS penetration of analgesics, enhanced norepinephrine release

Synergistic Effects:

The combination of paracetamol, diclofenac sodium, and caffeine produces:

1. **Enhanced Analgesic Effect:** Paracetamol + diclofenac provide dual analgesic action via different COX inhibition profiles; caffeine increases CNS penetration
2. **Improved Anti-inflammatory Action:** Diclofenac's potent anti-inflammatory effect combined with paracetamol's weaker peripheral effect
3. **Faster Onset:** Diclofenac sodium provides faster onset than diclofenac potassium; effervescent form enhances absorption
4. **Reduced Fatigue:** Caffeine counteracts the fatigue and lethargy often associated with pain conditions
5. **Extended Duration:** The three agents have different but overlapping pharmacokinetics, providing sustained pain relief

Efficacy Data:

- **Paracetamol + NSAIDs + Caffeine combination:** Superior efficacy to single agents or dual combinations
- **Headache relief:** Approximately 70-80% pain reduction at 2 hours (vs. 50-60% with dual combinations)
- **Dental pain:** Approximately 75-85% pain reduction (vs. 60-70% with single agents)
- **Musculoskeletal pain:** Sustained relief for 6-8 hours with improved functional capacity

5.2 Pharmacokinetic Properties

Absorption:

Paracetamol:

- **Route:** Oral (effervescent solution)
- **Tmax (time to peak concentration):** 30-60 minutes (faster than conventional tablets due to effervescent form)
- **Bioavailability:** 85-95% (first-pass metabolism minimal; ~5-10% lost to first-pass)
- **Absorption enhancement:** Effervescent formulation increases surface area and dissolves rapidly, enhancing absorption rate
- **pH effect:** Optimal absorption in neutral to slightly alkaline pH

Diclofenac Sodium:

- **Route:** Oral (effervescent solution)
- **Tmax:** 1-2 hours (sodium salt form provides faster absorption than potassium form; further enhanced by effervescent formulation)
- **Bioavailability:** 50-60% (significant first-pass metabolism)
- **Delayed-release characteristics:** Although this is immediate-release (effervescent), slower GI transit may reduce peak concentrations compared to buffered forms
- **Food interaction:** Minimal food effect; can be taken with or without food

Caffeine:

- **Route:** Oral (effervescent solution)
- **Tmax:** 30-60 minutes (rapid absorption from GI tract)
- **Bioavailability:** 95-98% (minimal first-pass metabolism)
- **Peak plasma concentration:** 2-4 μg/mL (from 30 mg dose)

Distribution:

Paracetamol:

- **Volume of Distribution (Vd):** 0.7-1.0 L/kg (body weight-dependent)
- **Protein binding:** <20% (minimal plasma protein binding)
- **Tissue penetration:** Good penetration into most tissues including CSF, though CSF penetration better in inflamed meninges
- **Placental crossing:** Crosses placenta; fetal concentrations approximately 95% of maternal concentrations

- **Breast milk penetration:** 0.04-0.23% of maternal dose

Diclofenac:

- **Volume of Distribution (Vd):** 1.4 L/kg (more extensive tissue distribution than paracetamol)
- **Protein binding:** 99% (highly protein-bound; increased risk of drug interactions through protein binding displacement)
- **Tissue penetration:** Excellent penetration into inflamed tissues where it accumulates; particularly high concentrations in synovial fluid
- **Synovial fluid concentrations:** Peak synovial concentrations reached 2-4 hours post-ingestion and persist longer than plasma concentrations
- **Placental crossing:** Crosses placenta; teratogenic in third trimester
- **Breast milk penetration:** 0.01% of maternal dose

Caffeine:

- **Volume of Distribution (Vd):** 0.5-0.7 L/kg (body weight-dependent)
- **Protein binding:** 25-36% (moderate protein binding)
- **Tissue penetration:** Rapidly crosses blood-brain barrier; crosses placenta freely
- **Breast milk penetration:** 0.06-1.5% of maternal dose (accumulates in nursing infants)

Metabolism:

Paracetamol:

- **Primary metabolic pathway:** Hepatic conjugation (90% of absorbed dose)
    - Sulfation: 40-60% (major pathway, saturable at high doses)
    - Glucuronidation: 30-50% (major pathway)
    - Oxidation (CYP2E1, CYP1A2, CYP3A4): 5-15% (produces toxic metabolite N-acetyl-p-benzoquinoneimine [NAPQI])
- **Minor pathways:** Acetylation, deacetylation
- **Toxic metabolite:** NAPQI is normally detoxified by glutathione conjugation; when glutathione is depleted (in overdose or chronic use), NAPQI accumulates causing hepatotoxicity
- **No active metabolites:** All metabolites are inactive
- **Genetic factors:** CYP2E1 polymorphisms affect metabolism rate; rapid metabolizers at higher risk in overdose, slow metabolizers at higher risk with chronic use

Diclofenac:

- **Primary metabolic pathway:** Hepatic oxidation
    - Hydroxylation: Major pathway via CYP2C9, CYP2C8, CYP3A4, producing 4-hydroxy and 5-hydroxy metabolites
    - Conjugation: Glucuronidation of parent drug and metabolites
    - Phase II metabolism: Sulfation, acetylation
- **Active metabolites:** Yes; 4-hydroxy-diclofenac retains some pharmacologic activity
- **Enterohepatic recirculation:** Yes; contributes to prolonged half-life despite rapid plasma clearance
- **CYP450 interactions:** Substrate of CYP2C9, CYP2C8, CYP3A4; risk of interactions with inhibitors and inducers

Caffeine:

- **Primary metabolic pathway:** Hepatic oxidation via CYP1A2 (80-90%)
    - N-demethylation: Produces paraxanthine (85% of caffeine metabolism)
    - Oxidation: Produces theobromine and theophylline (minor metabolites)
    - Acetylation: Minor pathway
- **Secondary metabolism:** Paraxanthine undergoes further metabolism to methyluric acids
- **No significant first-pass metabolism:** High bioavailability (95-98%)
- **CYP1A2 polymorphisms:** Genetic variants affect caffeine elimination; slow metabolizers (aa genotype) have prolonged half-lives; fast metabolizers (AA/Aa genotypes) have shorter half-lives
- **Active metabolites:** Paraxanthine has adenosine antagonist activity but lower potency than caffeine

Elimination:

Paracetamol:

- **Half-life (T½):** 2-3 hours (range: 1-4 hours depending on individual factors)
- **Renal elimination:** 85-90% of metabolites excreted in urine within 24 hours
- **Fecal elimination:** Minimal (<5%)
- **Biliary excretion:** Negligible
- **Factors affecting elimination:**
    - Renal impairment: Prolongs half-life
    - Hepatic impairment: Prolongs half-life significantly

- Enzyme induction (e.g., from chronic alcohol use, rifampicin): Accelerates metabolism
- Enzyme inhibition (e.g., from CYP2E1 inhibitors): Slows metabolism
- Age: Slightly prolonged in elderly

Diclofenac:

- **Half-life (T½):** 2 hours (plasma half-life, initial phase)
- **Terminal half-life:** 4-6 hours (due to enterohepatic recirculation and tissue sequestration)
- **Renal elimination:** 60-65% of metabolites excreted in urine within 24 hours
- **Biliary/Fecal elimination:** 35-40% via bile and enterohepatic recirculation
- **Plasma clearance:** High hepatic clearance (approximately 250 mL/min)
- **Factors affecting elimination:**
  - Renal impairment: Increases risk of toxicity
  - Hepatic impairment: Prolongs half-life
  - Elderly: Prolonged half-life due to reduced plasma clearance
  - CYP2C9 polymorphisms: *2/*3 variants associated with reduced metabolism

Caffeine:

- **Half-life (T½):** 2.5-5.5 hours (highly variable; range: 1.5-9.5 hours in some populations)
- **Renal elimination:** 2-5% unchanged caffeine
- **Metabolite elimination:** >95% of caffeine equivalents excreted in urine as metabolites
- **Biliary elimination:** Minimal
- **Factors affecting elimination:**
  - CYP1A2 polymorphisms: Major determinant (AA genotype: 1-2 hours; Aa: 2-5 hours; aa: 5-9 hours)
  - Smoking: Induces CYP1A2, accelerating elimination
  - Oral contraceptives: Inhibit CYP1A2, prolonging half-life (up to 10-20 hours)
  - Pregnancy: Prolonged half-life (up to 15-20 hours in third trimester)
  - Liver disease: Prolonged half-life
  - Renal disease: Minimal effect on elimination

Accumulation and Steady-State:

- **Paracetamol:** Minimal accumulation with appropriate dosing (6-8 hour intervals); steady-state achieved within 1-2 days
- **Diclofenac:** Possible accumulation with short dosing intervals; entero-hepatic recirculation prolongs elimination
- **Caffeine:** Significant inter-individual variability; may accumulate in slow metabolizers with frequent dosing; steady-state variable (1-5 days depending on genotype)

Special Populations:

Elderly Patients:

- Paracetamol: Slightly prolonged T½ (2.5-3.5 hours); reduced hepatic metabolism
- Diclofenac: Prolonged T½ (3-4 hours); reduced plasma clearance
- Caffeine: Prolonged T½; reduced renal clearance and metabolism

Renal Impairment (eGFR <60 mL/min):

- Paracetamol: Minimal effect on plasma T½; metabolites accumulate
- Diclofenac: T½ prolonged; risk of accumulation and toxicity
- Caffeine: Minimal effect on T½; metabolites may accumulate

Hepatic Impairment:

- Paracetamol: Significantly prolonged T½ (up to 4-8 hours); accumulation risk
- Diclofenac: Prolonged T½; risk of accumulation
- Caffeine: Prolonged T½; accumulation possible

5.3 Preclinical Safety Data

Acute Toxicity Studies:

Paracetamol:

- **LD50 (lethal dose 50%) - Oral:**
  - Rat: 300-350 mg/kg
  - Mouse: 350-500 mg/kg
  - Dog: >500 mg/kg (less susceptible due to different acetylation pathways)
- **Clinical relevance:** Estimated human lethal dose approximately 150-250 mg/kg (10-15 grams in 70 kg adult)
- **Mechanism:** Hepatotoxicity via glutathione depletion and NAPQI accumulation

Diclofenac:

- **LD50 - Oral:**
  - Rat: 150-200 mg/kg
  - Mouse: 150-300 mg/kg
- **Clinical relevance:** More toxic than paracetamol on weight basis
- **Mechanism:** GI ulceration and bleeding, cardiovascular collapse, acute kidney injury

Caffeine:

- **LD50 - Oral:**
  - Rat: 190-200 mg/kg
  - Mouse: 115-135 mg/kg
- **Clinical relevance:** Estimated human lethal dose approximately 100-200 mg/kg
- **Mechanism:** Seizures, cardiac arrhythmias, cardiovascular collapse

Subacute and Chronic Toxicity:

Paracetamol (28-90 day studies in rats):

- **NOAEL (No Observed Adverse Effect Level):** 250 mg/kg/day
- **Effects above NOAEL:** Hepatomegaly, elevated liver enzymes, histologic changes in liver
- **Hepatic fibrosis:** Observed at doses >500 mg/kg/day

Diclofenac (13-week studies in rats):

- **NOAEL:** 2-4 mg/kg/day
- **Effects above NOAEL:**
  - GI ulceration and bleeding
  - Renal papillary necrosis
  - Elevated BUN and creatinine
  - Hypertension
- **Chronic effects:** Enhanced GI ulceration with longer duration studies

Caffeine (90-day studies in rats):

- **NOAEL:** 20-50 mg/kg/day
- **Effects above NOAEL:** Increased body weight loss, reduced food intake, cardiac hypertrophy
- **Reproductive toxicity:** No adverse effects on fertility at NOAELs

Genotoxicity (Mutagenicity):

Paracetamol:

- **Ames test:** Negative
- **In vitro chromosomal aberration test:** Negative
- **In vivo micronucleus test:** Negative
- **Conclusion:** No genotoxic potential

Diclofenac:

- **Ames test:** Negative
- **In vitro chromosomal aberration test:** Negative (in mammalian cells)
- **In vivo micronucleus test:** Negative
- **Conclusion:** No genotoxic potential

Caffeine:

- **Ames test:** Positive at very high concentrations (>5 mmol/L); not observed at physiologically relevant doses
- **In vitro chromosomal aberration test:** Negative at therapeutic concentrations
- **In vivo micronucleus test:** Negative
- **Conclusion:** No genotoxic potential at therapeutic doses; positive results only at supratherapeutic concentrations

Reproductive and Developmental Toxicity:

Paracetamol:

- **Fertility studies (rat, 8 weeks):** No adverse effects on fertility
- **Developmental toxicity studies:**
  - **Rat (GD6-15):** NOAEL 300 mg/kg/day; no teratogenic effects
  - **Rabbit (GD6-18):** NOAEL 150 mg/kg/day; no teratogenic effects
- **Clinical relevance:** FDA Category B (human evidence of safety)

Diclofenac:

- **Fertility studies (rat, 11 weeks):** Effects on sexual function and fertility at doses >3 mg/kg/day (reduced mating and fertility)
- **Developmental toxicity studies:**
  - **Rat (GD6-15):** NOAEL 1 mg/kg/day; increased fetal loss at higher doses
  - **Rabbit (GD6-18):** NOAEL 2 mg/kg/day; teratogenic effects (skeletal abnormalities, ductus arteriosus closure) at higher doses
- **Clinical relevance:** Contraindicated in third trimester; caution in first and second trimester

Caffeine:

- **Fertility studies (rat, 10 weeks):** No effects on fertility at doses up to 50 mg/kg/day
- **Developmental toxicity studies:**
  - **Rat (GD6-15):** NOAEL 50 mg/kg/day; cleft palate and growth retardation at >80 mg/kg/day
  - **Rabbit (GD6-18):** NOAEL 10 mg/kg/day; skeletal effects at higher doses
- **Clinical relevance:** Use with caution during pregnancy; some evidence of increased miscarriage at high doses

Carcinogenicity:

Paracetamol:

- **2-year rat study (oral):** No evidence of carcinogenicity at doses up to 1500 mg/kg/day
- **2-year mouse study (oral):** No evidence of carcinogenicity at doses up to 1500 mg/kg/day
- **Classification:** IARC Group 3 (not classifiable as carcinogenic)

Diclofenac:

- **Lifetime rat study:** No evidence of carcinogenicity at doses up to 4 mg/kg/day
- **Lifetime mouse study:** No evidence of carcinogenicity
- **Classification:** No evidence of carcinogenic potential

Caffeine:

- **Lifetime rat/mouse studies:** No evidence of carcinogenicity at doses up to 100 mg/kg/day
- **IARC classification:** Group 2B (possibly carcinogenic to humans) based on limited evidence
- **Clinical relevance:** No increased cancer risk observed in epidemiologic studies at normal consumption levels

Other Toxicity Studies:

Local Tolerance (Oral):

- All three active ingredients have been demonstrated to be tolerable when administered orally
- No local irritation observed in animal studies at therapeutic doses
- Effervescent formulation may cause minor local irritation in sensitive oral mucosa

Immunotoxicity:

- Paracetamol: Minimal effect on immune function at therapeutic doses; high doses may suppress cellular immunity
- Diclofenac: May suppress immune responses through PGE2 inhibition; clinical significance unclear
- Caffeine: No significant immunotoxic effects at therapeutic doses

Environmental Toxicity:

- All three substances have potential aquatic toxicity; not of immediate concern for clinical use
- Bioaccumulation potential: Low for all three substances

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Excipients used in TRIAQUI-DF® Effervescent Tablets:

Excipient	Function	Quantity per tablet (mg)
Sodium Bicarbonate (Sodium Hydrogen Carbonate, BP)	Effervescent agent, pH buffer	400
Citric Acid Monohydrate (BP)	Effervescent agent, acidifying agent	280
Sorbitol (BP/USP)	Sweetening agent, diluent	300
Sodium Saccharin (BP/USP)	Artificial sweetener	20
Sucralose (INN)	High-intensity sweetener	5
Povidone K30 (Polyvinylpyrrolidone, BP/USP)	Binder, tablet disintegrant	40
Sodium Starch Glycolate (BP/USP)	Tablet disintegrant	30
Magnesium Stearate (BP/USP)	Lubricant, flow agent	10
Colloidal Anhydrous Silica (Aerosil®, BP/USP)	Flow agent, anti-caking agent	8

Orange Flavor (INN, Natural & Artificial)	Flavor enhancer	12
Tartaric Acid (BP/USP)	pH adjuster, acidifying agent	5
FD&C Yellow No. 6 (Sunset Yellow FCF, E110, BP/USP)	Colorant	2
FD&C Red No. 40 (Allura Red AC, E129, BP/USP)	Colorant	1

Total weight per tablet: Approximately 4.5 grams

For a full list of excipients, see section 6.1.

Excipient Justification:

Sodium Bicarbonate and Citric Acid:

- Form the effervescent system that produces CO2 gas when dissolved in water
- Ratio optimized (sodium bicarbonate:citric acid ≈ 1.4:1) to ensure complete reaction and provide buffering capacity
- Support rapid dissolution and faster bioavailability of active ingredients

Sorbitol:

- Non-nutritive sweetener with good solubility
- Prevents crystallization and caking during storage
- Contributes to palatability without aftertaste

Sodium Saccharin and Sucralose:

- Dual sweetener system provides improved taste profile
- Sucralose has higher sweetness intensity (600× sucrose), allowing lower total sweetener content
- Combination masks bitter taste of diclofenac

Povidone K30:

- Acts as binding agent during tablet compression
- Enhances dissolution rate by increasing wettability
- Improves flow properties

Sodium Starch Glycolate:

- Rapid-swelling disintegrant enhances tablet disintegration in water
- Particularly important for effervescent tablets to ensure complete dissolution within 2-3 minutes
- Also prevents tablet caking

Magnesium Stearate:

- Lubricant prevents tablet sticking to punch and die during compression
- Used at minimum effective concentration to maintain dissolution characteristics
- Quantity ≤10 mg/tablet ensures it does not negatively impact tablet disintegration

Colloidal Anhydrous Silica:

- Anti-caking agent prevents agglomeration during storage
- Improves powder flow during tableting
- Helps maintain tablet hardness and stability

Orange Flavor:

- Natural and artificial flavor components provide pleasant taste
- Masks medicinal taste of active ingredients
- Naturally stable in acidic environment of effervescent tablet

Tartaric Acid:

- Provides additional pH buffering
- Contributes to effervescent action
- Enhances acidic flavor profile

Colorants (FD&C Yellow No. 6 and Red No. 40):

- FD&C Yellow No. 6 (E110 - Sunset Yellow) provides yellow coloration
- FD&C Red No. 40 (E129 - Allura Red) provides red coloration
- Combined produce orange-colored solution upon dissolution
- Approved for use in pharmaceutical preparations in US, EU, and other regions
- Allow patient identification and improve acceptability

Excipient Specifications:

All excipients conform to:

- British Pharmacopoeia (BP) or United States Pharmacopoeia (USP) standards where available
- Or European Pharmacopoeia (Ph.Eur.) standards
- Certificate of Analysis provided for each batch

Known Sensitivities:

- **Sucralose:** Generally well-tolerated; phenylketonuria patients should be aware saccharin may be present as alternative sweetener
- **Colorants:** FD&C dyes may trigger sensitivity in individuals with artificial color sensitivity or certain food additives sensitivities (documented in pediatric ADHD literature)
- **Povidone:** Rarely causes allergic reactions; cross-reactivity with other polymers possible
- **Magnesium Stearate:** May cause mild gastrointestinal effects if taken in large quantities; normal tablet quantity poses minimal risk

6.2 Incompatibilities

TRIAQUI-DF® Effervescent Tablets should not be mixed with:

1. **Milk or dairy products:** Calcium in milk may complex with diclofenac reducing bioavailability
2. **Alcohol (ethanol) solutions or suspensions:** Risk of enhanced GI toxicity and hepatotoxicity
3. **Other effervescent medications:** Unpredictable pH and osmolarity changes
4. **Antacids containing aluminum or magnesium hydroxide:** May bind diclofenac and reduce absorption
5. **Ferrous sulfate or iron supplements:** May form complexes with diclofenac
6. **Strong oxidizing agents:** May cause degradation of active ingredients

Storage conditions preventing incompatibility:

- Do not store in humid environments (humidity >60%)
- Store in air-tight, moisture-proof containers
- Keep away from direct sunlight
- Do not store near heat sources

6.3 Shelf Life

Storage Conditions:

- **Temperature:** Store at temperature not exceeding 30°C (room temperature)
- **Humidity:** Store in a dry place; relative humidity not exceeding 60%
- **Light:** Protect from direct light in original packaging

Shelf Life: 36 months (3 years) from date of manufacture when stored in specified conditions

After Opening:

- Use within 6 months if container is opened
- After opening, tablets should be used immediately or bottle should be re-sealed promptly
- If exposed to excessive moisture, tablet appearance may change (browning at edges); product should be discarded

Appearance Change Indicators (product should be discarded):

- Tablets showing brown discoloration at edges or surfaces
- Tablets showing hardening or increased brittleness
- Loss of fragrance or change in odor
- Excessive tablet breakage or powderiness upon handling

6.4 Nature and Contents of Container

Primary Packaging:

Container Type: Aluminum laminate blister strips (Aluminum-Aluminum or Aluminum-PVC)

Specifications:

- **Front side:** Clear PVC (Polyvinyl Chloride) film (80 µm thickness)
    - Allows visual inspection of tablets
    - Provides moderate moisture barrier
- **Back side:** Aluminum foil (40 µm thickness)
    - Soft aluminum providing superior moisture and light barrier
    - Printed with product information, batch number, expiry date, manufacturing date
- **Cavity depth:** 12 mm, customized for tablet size (19 mm diameter)
- **Individual cavities:** Separated by foil matrix preventing cross-contamination

Pack Sizes:

Pack Size	Configuration	Blister format
10 tablets	1 × 10	Single strip of 10 cavities
15 tablets	1 × 15	Single strip of 15 cavities
20 tablets	2 × 10	Two strips of 10 cavities each
20 tablets	1 × 20	Single strip of 20 cavities
30 tablets	3 × 10	Three strips of 10 cavities each
40 tablets	4 × 10	Four strips of 10 cavities each
50 tablets	5 × 10	Five strips of 10 cavities each
60 tablets	6 × 10	Six strips of 10 cavities each
100 tablets	10 × 10	Ten strips of 10 cavities each (institutional pack)

Not all pack sizes may be marketed.

Secondary Packaging:

For Consumer Packs (≤60 tablets):

- **Type:** Cardboard carton (250-300 gsm white kraft cardboard)
- **Dimensions:** Tailored to accommodate primary blister
- **Printing:** 4-color process printing on exterior
- **Contents:**
    - Product blister(s)
    - Leaflet (Patient Information Leaflet - PIL)
    - Desiccant packet (silica gel, 2-5 grams) if desired
    - Product code sticker/label

For Institutional/Bulk Packs (>60 tablets):

- **Type:** Corrugated cardboard case
- **Dimensions:** Customized based on number of blisters
- **Compartmentalization:** Individual blisters arranged in organized manner
- **Cushioning:** Foam inserts or cardboard partitions
- **Sealing:** Adhesive tape or automated sealing
- **External labeling:** Comprehensive label including:
    - Product name, strength, pharmaceutical form
    - Lot/Batch number
    - Manufacturing date and expiry date
    - Storage conditions
    - Quantity and pack configuration
    - Manufacturer and distributor information

Storage Container for Opened Package:

Patients who open the blister should be advised to:

- Store remaining tablets in original blister in a cool, dry place
- Keep tablets in original packaging to maintain moisture barrier
- Do not transfer to other containers (e.g., pill organizers) as this exposes tablets to moisture and light
- Use remaining tablets within 6 months of opening

6.5 Nature and Contents of the Container - Special Equipment

No special equipment is required for administration. The tablets are dissolved in water and consumed orally, requiring only:

- A clean glass or cup (capacity ≥200 mL)
- Potable water (approximately 100-150 mL per tablet)
- A spoon (for mixing, optional)

No other devices required for proper use and administration.

6.6 Special Precautions for Disposal

Disposal of Unused Medicinal Product or Waste Derived Therefrom:

Patient Disposal:

Households:

1. **Check local regulations:** Many countries have specific programs for disposal of unused medications
2. **Pharmacy take-back programs:** Most pharmacies and drugstores have programs to safely dispose of unused medications
    - Return unused tablets in original blister
    - No charge to patient
    - Most environmentally and safety-responsible method
3. **Home disposal (if pharmacy take-back unavailable):**
    - Mix tablets with unpalatable substance (e.g., coffee grounds, salt) in a sealable bag
    - Place mixture in sealed bag, then in household trash
    - Never flush tablets down toilet unless explicitly marked as "flushable" (this formulation is NOT flushable)
    - Do not dispose in drain or waterway
4. **Child-resistant disposal:** Ensure disposal is away from reach of children

Healthcare Facilities:

- Follow institutional guidelines for pharmaceutical waste disposal
- Generally disposed through licensed medical waste management companies
- Incineration at ≥800°C or chemical treatment may be used

Environmental Considerations:

- **DO NOT flush down toilets or drains** - this formulation contains ingredients that may have aquatic toxicity
- **DO NOT dispose in landfills** without sealing in non-permeable containers
- **DO NOT pour liquid solutions of dissolved tablets into waterways**
- Proper disposal prevents water contamination and potential environmental harm

Regulatory Compliance:

- Disposal should comply with local and national regulations
- In EU countries, follow directives on hazardous waste disposal
- In US, follow FDA and EPA guidelines on pharmaceutical disposal
- In India, follow Central Pollution Control Board (CPCB) guidelines

7. MARKETING AUTHORISATION HOLDER

7.1 Marketing Authorisation Holder (MAH)

Company Name: PHARMA-SOLUTIONS EUROPE GmbH

Registered Address:
Pharmastrasse 47-51
D-80686 Munich
Bavaria
Federal Republic of Germany

Company Registration Number: HRB 298174 (Munich Commercial Register)

Phone: +49 (0)89 555-0123

Email: regulatory@pharma-solutions.de

Website: www.pharma-solutions.de

Regulatory Contact: Dr. Friedrich Weber, Head of Regulatory Affairs

7.2 Manufacturing Facility Details

Primary Manufacturing Facility:

Name: PHARMA-SOLUTIONS EUROPE GmbH - Manufacturing Division

Address:
Produktionsweg 8-12
I-20024 Milan (Lombardy)
Provincia di Milano
Republic of Italy

GPS Coordinates: 45.4642° N, 9.1900° E

Facility Registration: Italian Ministry of Health - AIFA Registration No. IT-MAN-2024-0847

8. MARKETING AUTHORISATION NUMBER(S)

Country/Region	Authorization Number	Format	Issue Date	Expiry Date
Germany	BfArM/2024/DE-00567	DE/2024/567	January 15, 2024	January 14, 2029
Italy	AIFA/2024/IT-00423	IT/2024/423	February 20, 2024	February 19, 2029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First Authorization Date: January 15, 2024

Marketing Authorization Holder: PHARMA-SOLUTIONS EUROPE GmbH

Authority Granting First Authorization: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM - German Federal Institute for Drugs and Medical Devices)

Renewal Status:

- Authorization period: 5 years from issue date
- First Renewal Anticipated: January 2029
- Current Valid Authorization Period: January 15, 2024 - January 14, 2029

Post-Authorization Changes:

- Quality Overall Summary (CMC) submitted to competent authorities annually
- Periodic Safety Update Report (PSUR) submitted every 6 months during first 2 years of marketing, then annually
- Annual Report submitted to all marketing authorization holders documenting any changes to formulation, manufacturing process, or labeling

10. DATE OF REVISION OF THE TEXT

Version Number: 1.2

Revision Date: December 15, 2024

Changes in Version 1.2:

- Updated adverse reactions frequency data based on post-marketing surveillance data from German and Italian markets (January-November 2024)
- Added clarification on maximum daily caffeine intake recommendation
- Expanded drug interaction section to include additional information on QT-prolonging agents
- Added information on availability in additional EU member states (Poland, Czech Republic)

Previous Version: 1.1 (Issued: September 1, 2024)

Approval Authority: AIFA (Agenzia Italiana del Farmaco - Italian Medicines Agency)