

### **1.3.1 Summary of Product Characteristics (SmPC)**

#### **1. Name of the medicinal Product**

**a) Product Name: Ketorolac Tromethamine Dispersible Tablets 10mg**

**b) Strength:**

Each uncoated dispersible tablet contains:

Ketorolac Tromethamine USP.....10mg

**c) Pharmaceutical Dosage form**

Solid dosage form (Oral Tablets)

#### **2. Quality and Quantitative Composition**

**a) Qualitative declaration**

Ketorolac Tromethamine USP.....10mg

**b) Quantitative declaration**

Each uncoated dispersible tablet contains:

Ketorolac Tromethamine USP.....10mg

#### **3. Pharmaceutical form visual description of the appearance of the product**

Orange coloured, round shaped, flat, scored on one side uncoated tablets.

#### **4. Clinical Particulars**

##### **4.1 Therapeutic indications**

Ketorolac Tromethamine Dispersible Tablets 10mg is indicated for the short-term management of moderate to severe acute post-operative pain.

The maximum duration of treatment is not to exceed five days.

##### **4.2 Posology and method of administration:**

###### **Dosing Considerations**

Use of ketorolac tromethamine should be limited to the lowest effective dose for the shortest possible duration of treatment.

Adults

The recommended initial dose of Ketorolac Tablets is 10mg, followed by 10 to 30mg every four to six hours as required. A total daily dose of 90mg for non-elderly and 60mg for the elderly, renally-impaired patients and patients less than 50kg should not be exceeded. The maximum duration of treatment should not exceed five days.

### **4.3 Contraindications**

Ketorolac tromethamine is contraindicated in patients with previously demonstrated hypersensitivity to ketorolac tromethamine.

Ketorolac tromethamine is contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Ketorolac tromethamine should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

Ketorolac tromethamine is contraindicated as prophylactic analgesic before any major surgery.

Ketorolac tromethamine is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

Ketorolac tromethamine is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events.

The concomitant use of ketorolac tromethamine and probenecid is contraindicated.

The concomitant use of ketorolac tromethamine and pentoxifylline is contraindicated.

### **4.4 Special warning and precautions for use**

#### **WARNINGS**

##### **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**

Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or GI bleeding. Ketorolac tromethamine can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration and perforation, of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. Do not use ketorolac tromethamine for more than five days. However, even short-term therapy is not without risk.

In addition to past history of ulcer disease, other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids, or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

**To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of ketorolac tromethamine until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

### **Hemorrhage**

Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and therapy that affects hemostasis, including prophylactic low-dose heparin (2500 to 5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks and use such concomitant therapy in these patients only extremely cautiously. Patients receiving therapy that affects hemostasis should be monitored closely.

### **Renal Effects**

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired

renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

### **Cardiovascular Effects**

#### **Cardiovascular Thrombotic Events**

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

### **PRECAUTIONS**

#### **General**

Ketorolac tromethamine cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of ketorolac tromethamine in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

#### **Hepatic Effect**

Ketorolac tromethamine should be used with caution in patients with impaired hepatic function or a history of liver disease. Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including ketorolac tromethamine. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test

has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketorolac tromethamine. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ketorolac tromethamine should be discontinued.

#### **Hematologic Effect**

Anemia is sometimes seen in patients receiving NSAIDs, including ketorolac tromethamine. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ketorolac tromethamine, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ketorolac tromethamine who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

#### **Preexisting Asthma**

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ketorolac tromethamine should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

### **4.5 Interaction with other medicinal products and other forms of Interactions**

#### **Aspirin**

When ketorolac tromethamine is administered with aspirin, its protein binding is reduced, although the clearance of free ketorolac tromethamine is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ketorolac tromethamine and aspirin is not generally recommended because of the potential of increased adverse effects.

#### **Diuretics**

Clinical studies, as well as postmarketing observations, have shown that ketorolac tromethamine can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the

patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

#### Probenecid

Concomitant administration of ketorolac tromethamine tablets and probenecid resulted in decreased clearance and volume of distribution of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately threefold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately twofold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

#### Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

#### Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

#### ACE Inhibitors/Angiotensin II Receptor Antagonists

Concomitant use of *ACE inhibitors and/or angiotensin II receptor antagonists* may increase the risk of renal impairment, particularly in volume-depleted patients.

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors and/or angiotensin II receptor antagonists. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors and/or angiotensin II receptor antagonists.

#### Antiepileptic Drugs

Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and antiepileptic drugs (phenytoin, carbamazepine).

#### Psychoactive Drugs

Hallucinations have been reported when ketorolac tromethamine was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam).

#### Pentoxifylline

When ketorolac tromethamine is administered concurrently with pentoxifylline, there is an increased

tendency to bleeding.

#### Nondepolarizing Muscle Relaxants

In postmarketing experience there have been reports of a possible interaction between ketorolac tromethamine IV/IM and nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

### **4.6 Pregnancy and lactation**

#### Teratogenic Effects

##### *Pregnancy Category C*

Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. However, animal reproduction studies are not always predictive of human response.

#### Nonteratogenic Effects

Because of the known effects of non-steroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation Day 17, caused dystocia and higher pup mortality in rats.

There are no adequate and well-controlled studies of ketorolac tromethamine in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Limited data from one published study involving 10 breastfeeding women 2 to 6 days postpartum showed low levels of ketorolac in breast milk. Levels were undetectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 mg of ketorolac tromethamine tablets, the maximum milk concentration observed was 7.3 ng/mL, and the maximum milk-to-plasma ratio was 0.037. After 1 day of dosing (10 mg every 6 hours), the maximum milk concentration was 7.9 ng/mL, and the maximum milk-to-plasma ratio was 0.025. Assuming a daily intake of 400 to 1,000 mL of human milk per day and a maternal body weight of 60 kg, the calculated maximum daily infant exposure was 0.00263 mg/kg/day, which is 0.4% of the maternal weight-adjusted dose.

Exercise caution when ketorolac is administered to a nursing woman. Available information has not shown any specific adverse events in nursing infants; however, instruct patients to contact their infant's health care provider if they note any adverse events.

#### **4.7 Effects on ability to drive and use machine**

Clinical experience with ketorolac tromethamine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

#### **4.8 Undesirable effects**

Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as GI ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure. These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

In patients taking ketorolac tromethamine or other NSAIDs in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

Gastrointestinal (GI) experiences including:		
abdominal pain *	constipation/diarrhea	dyspepsia *
flatulence	GI fullness	GI ulcers (gastric/duodenal)
gross bleeding/perforation	heartburn	nausea *
stomatitis	vomiting	
Other experiences:		
abnormal renal function	anemia	dizziness
drowsiness	edema	elevated liver enzymes
headaches *	hypertension	increased bleeding time
injection site pain	pruritus	purpura
rashes	tinnitus	sweating
* Incidence greater than 10%		

Additional adverse experiences reported occasionally (< 1% in patients taking ketorolac tromethamine or other NSAIDs in clinical trials) include:

**Body as a Whole:** fever, infections, sepsis

**Cardiovascular:** congestive heart failure, palpitation, pallor, tachycardia, syncope

**Dermatologic:** alopecia, photosensitivity, urticaria

**Gastrointestinal:** anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, rectal bleeding



**Hemic and Lymphatic:** ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia

**Metabolic and Nutritional:** weight change

**Nervous System:** abnormal dreams, abnormal thinking, anxiety, asthenia, confusion, depression, euphoria, extrapyramidal symptoms, hallucinations, hyperkinesis, inability to concentrate, insomnia, nervousness, paresthesia, somnolence, stupor, tremors, vertigo, malaise

**Reproductive, female:** infertility

**Respiratory:** asthma, cough, dyspnea, pulmonary edema, rhinitis

**Special Senses:** abnormal taste, abnormal vision, blurred vision, hearing loss

**Urogenital:** cystitis, dysuria, hematuria, increased urinary frequency, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure, urinary retention

Other rarely observed reactions (reported from postmarketing experience in patients taking ketorolac tromethamine or other NSAIDs) are:

**Body as a Whole:** angioedema, death, hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema, myalgia

**Cardiovascular:** arrhythmia, bradycardia, chest pain, flushing, hypotension, myocardial infarction, vasculitis

**Dermatologic:** exfoliative dermatitis, erythema multiforme, Lyell's syndrome, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

**Gastrointestinal:** acute pancreatitis, liver failure, ulcerative stomatitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease)

**Hemic and Lymphatic:** agranulocytosis, aplastic anemia, hemolytic anemia, lymphadenopathy, pancytopenia, postoperative wound hemorrhage.

**Metabolic and Nutritional:** hyperglycemia, hyperkalemia, hyponatremia

**Nervous System:** aseptic meningitis, convulsions, coma, psychosis

**Respiratory:** bronchospasm, respiratory depression, pneumonia

**Special Senses:** conjunctivitis

**Urogenital:** flank pain with or without hematuria and/or azotemia, hemolytic uremic syndrome

#### **4.9 Overdose**

##### **Signs and Symptoms:**

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

##### **Treatment**

Patients should be managed by symptomatic and supportive care following a NSAIDs overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 g to 100 g in adults, 1 g/kg to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large oral overdose (5 to 10 times the usual dose). Forced diuresis, alkalization of urine, hemodialysis or hemoperfusion may not be useful due to high protein binding. Single overdoses of ketorolac tromethamine have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing.

#### **5. Pharmacological Properties:**

##### **5.1 Pharmacodynamic Properties**

**Pharmacotherapeutic group:** Non steroidal anti-inflammatory drug (NSAID)

Mechanism of action

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models. The mechanism of action of ketorolac, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

The peak analgesic effect of ketorolac tromethamine occurs within 2 to 3 hours and is not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine is in the duration of analgesia.

## **5.2 Pharmacokinetic properties**

### **Absorption**

Ketorolac tromethamine is 100% absorbed after oral administration. Oral administration of ketorolac tromethamine after a high-fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

### **Distribution**

The mean apparent volume ( $V_{\beta}$ ) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single-dose data. The ketorolac tromethamine racemate has been shown to be highly protein bound (99%). Nevertheless, plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites.

### **Metabolism**

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

### **Excretion**

The principal route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg ketorolac tromethamine ( $n = 9$ ) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans.

## **5.3 Preclinical safety data**

Preclinical information has not been included because the safety profile of ketorolac tromethamine been established after many years of clinical use.

## **6. Pharmaceutical Particulars:**

### **6.1 List of excipients :**

Mannitol

Colloidal Anhydrous Silica

Butylated Hydroxyanisole

Polyplasdone XL (Crospovidone)

Isopropyl Alcohol

Neotame

Sweet orange Flavour

Lake Sunset Yellow colour

Croscarmellose Sodium

Magnesium Stearate

## **6.2 Incompatibilities**

Not applicable

## **6.3 Shelf life**

Shelf-life: 24-months

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

1x10 Tablets Alu-Alu Blister packed in mono carton along with package insert such 10 monocarton packed in a outer carton.

## **6.6 Special precautions for disposal <and other handling>**

Not Applicable

## **7.0 Applicant/Manufacturer**

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