## 1. Name of the medicinal product

Ketolac

## 2. Qualitative and quantitative composition

Ketorolac tromethamine 10mg

## 3. Pharmaceutical form

Tablet

## 4. Clinical particulars

### 4.1 Therapeutic indications

Ketolac tablet is used in the management of acute and severe pains

### 4.2 Posology and method of administration

Adults:

20 mg to be taken once followed by 10 mg every 4-6 hours when necessary, **not greater than 40 mg/day.**

*Paediatric population*

Not indicated for paediatric use.

*Method of administration*

Oral

### 4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

The potential exists for cross-sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs. Ketolac is contraindicated in individuals who have previously exhibited sensitivities to these drugs.

### 4.4 Special warnings and precautions for use

It is recommended that this drug be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

All non-steroidal anti-inflammatory drugs (NSAIDs) may slow down or delay wound healing. Concomitant use of NSAIDs and topical steroids can increase the potential for healing problems.

There have been post-marketing reports of bronchospasm or exacerbation of asthma in patients, who have either a known hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs or a past medical history of asthma associated with the use of ketorolac tromethamine, which may be contributory. Caution is recommended in the use of ketorolac tromethamine in these individuals.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

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

**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 post marketing 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.

**Probenecid**

Concomitant administration of ketorolac tromethamine and ***probenecid*** resulted in decreased clearance and volume of distribution of ketorolac and significant increases in ketorolac plasma levels. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

**4.6 Fertility, pregnancy and lactation**
Pregnancy

There are no adequate data from the use of eye drops containing ketorolac tromethamine in pregnant women. Studies in animals have shown reproductive toxicity. Inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/foetal development and/ or postnatal development. Ketorolac tromethamine is not recommended during pregnancy.

Breast-feeding

Ketorolac tromethamine should not be used during breast-feeding. Ketorolac tromethaminel is excreted in human milk after systemic administration.

Fertility

There are no adequate data from the use of ketorolac tromethamine on fertility in humans.

**4.7 Effects on ability to drive and use machines**
Transient blurring of vision may occur on taking this drug. Do not drive or use hazardous machinery unless vision is clear.

**4.8 Undesirable effects**
The frequency of adverse reactions documented during clinical trials of ketorolac tromethamine and through post-marketing experience is given below and is defined as follows:

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000); Not Known (cannot be estimated from available data).

| | |
|---|---|
| *Immune system disorders* | |
| Common: | Hypersensitivity including localised allergic reactions |
| *Nervous system disorders* | |
| Common: | Headache |
| *Eye Disorders* | |
| Very Common: | Eye irritation (including burning sensation)<br>Eye pain (including stinging) |
| Uncommon: | Corneal ulcer<br>Corneal infiltrates<br>Eye dryness<br>Epiphora |
| Not known: | Corneal damage, e.g. thinning, erosion, epithelial breakdown and perforation*<br>ulcerative keratitis<br>eye swelling<br>ocular hyperaemia |
| *Respiratory, thoracic and mediastinal disorders* | |
| Not known: | Bronchospasm or exacerbation of asthma** |

## 4.9 Overdose

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.

**5. Pharmacological properties**

**Pharmacodynamics**

Ketorolac tromethamine is a nonsteroidal 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.

**Absorption**

ketorolac tromethamine is 100% absorbed after oral administration. Oral administration 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 (Vβ) 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 µg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

**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.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

# 6. Pharmaceutical particulars

**6.1 List of excipients**
Calcium phosphate dibasic, microcrystalline cellulose, cross povidone, magnesium stearate,

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
**6.4 Special precautions for storage**
Store below 30° C

**6.5 Nature and contents of container**
**Blister pack of 1x10 tablets**

**6.6 Special precautions for disposal and other handling**
No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. Marketing authorization holder**

**Amriya Pharmaceuticals Ind.**

**Km 25, Alexandria Cairo Desert, Egypt**