

1. Name of the medicinal product

INN Name: Ketorolac Tromethamine Injection 30 mg/mL

Trade Name: ACUDOL 30

Strength: 30 mg/mL

Pharmaceutical form: Injection

2. Qualitative and quantitative composition

Each mL contains 30 mg of Ketorolac Tromethamine.

3. Pharmaceutical form

Dosage form: Injection

Description: A clear and slight yellow solution, in 2mL Type-I, amber color tubular glass vial with 13mm grey bromobutyl rubber stopper and 13mm orange color flip off aluminum seal.

4. Clinical particulars

4.1 Therapeutic indications

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in adults.

Acute Pain in Adult Patients

Ketorolac tromethamine is indicated for the short-term (≤ 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with IV or IM dosing of ketorolac tromethamine, and oral ketorolac tromethamine is to be used only as continuation treatment, if necessary.

The total combined duration of use of ketorolac tromethamine injection and oral ketorolac tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients

should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

Ketorolac tromethamine injection has been used concomitantly with morphine and meperidine and has shown an opioid-sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the ketorolac tromethamine injection dosage range with low doses of narcotics prn, unless otherwise contraindicated. Ketorolac tromethamine injection and narcotics should not be administered in the same syringe

4.2 Posology and method of administration

Posology

Carefully consider the potential benefits and risks of ketorolac tromethamine and other treatment options before deciding to use ketorolac tromethamine. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. In adults, the combined duration of use of IV or IM dosing of ketorolac tromethamine and oral ketorolac tromethamine is not to exceed 5 days. In adults, the use of oral ketorolac tromethamine is only indicated as continuation therapy to IV or IM dosing of ketorolac tromethamine.

- Note: Oral formulation should not be given as an initial dose.
- Use minimum effective dose for the individual patient.
- Total duration of treatment in adult patients: the combined duration of use of IV or IM dosing of ketorolac tromethamine and oral ketorolac tromethamine is not to exceed 5 days.
- Missed doses
- Patients should be instructed that, if they miss a dose of Daclatasvir dihydrochloride, the dose should be taken as soon as possible if remembered within 20 hours of the scheduled dose time. However, if the missed dose is remembered more than 20 hours after the scheduled dose, the dose should be skipped and the next dose taken at the appropriate time.
- Special populations
- Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs.) of body weight and for patients with moderately elevated serum creatinine

Doses of ketorolac tromethamine injection are not to exceed 60 mg (total dose per day) in these patients.

Method of administration

Ketorolac tromethamine injection may be used as a single or multiple dose on a regular or “prn” schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine. Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

When administering ketorolac tromethamine injection, the IV bolus must be given over no less than 15 seconds. The IM administration should be given slowly and deeply into the muscle. The analgesic effect begins in ~30 minutes with maximum effect in 1 to 2 hours after dosing IV or IM. Duration of analgesic effect is usually 4 to 6 hours.

Single-Dose Treatment: The following regimen should be limited to single administration use only IM Dosing

- Patients <65 years of age: One dose of 60 mg.
- Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 30 mg.

IV Dosing

- Patients <65 years of age: One dose of 30 mg.
- Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 15 mg.

Multiple-Dose Treatment (IV or IM)

- Patients <65 years of age: The recommended dose is 30 mg ketorolac tromethamine injection every 6 hours. The maximum daily dose for these populations should not exceed 120 mg.
- For patients ≥65 years of age, renally impaired patients, and patients less than 50 kg (110 lbs): The recommended dose is 15 mg ketorolac tromethamine injection every 6 hours. The maximum daily dose for these populations should not exceed 60 mg.

For breakthrough pain, do not increase the dose or the frequency of ketorolac tromethamine. Consideration should be given to supplementing these regimens with low doses of opioids “prn” unless otherwise contraindicated.

Pharmaceutical Information for Ketorolac Tromethamine Injection

Ketorolac tromethamine injection should not be mixed in a small volume (e.g., in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

4.3 Contraindications

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

Ketorolac tromethamine inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding .

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.

Ketorolac tromethamine injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.

4.4 Special warnings and precautions for use

The total combined duration of use of oral ketorolac tromethamine and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients.

The most serious risks associated with ketorolac tromethamine are:

- **Gastrointestinal Effects – Risk of Ulceration, Bleeding and Perforation:**

Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or gastrointestinal (GI) bleeding. Ketorolac tromethamine can cause serious 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 - 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.

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the peri-operative use of IV or IM dosing of ketorolac tromethamine.

Therefore, peri-operative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical .

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.

Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug. Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, interstitial nephritis and nephrotic syndrome.

Impaired Renal Function

Ketorolac tromethamine is contraindicated in patients with serum creatinine concentrations indicating advanced renal impairment. Ketorolac tromethamine should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Because patients with underlying renal insufficiency are at increased risk of developing acute renal decompensation or failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ketorolac tromethamine. Ketorolac tromethamine should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS – Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

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.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation). Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke .

Hypertension

NSAIDs, including ketorolac tromethamine, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ketorolac tromethamine, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension or similar conditions.

Skin Reactions

NSAIDs, including ketorolac tromethamine, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, ketorolac tromethamine should be avoided because it may cause premature closure of the ductus arteriosus.

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 Effects

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 Effects

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.

Pre-existing 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 nonsteroidal 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 pre-existing asthma.

Information for Patients

Ketorolac tromethamine is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing ketorolac tromethamine, should inform their patients or their guardians of the potential risks of ketorolac tromethamine treatment, instruct patients to seek medical advice if they develop treatment-related adverse events, and advise patients not to give oral ketorolac tromethamine to other family members and to discard any unused drug.

Remember that the total combined duration of use of oral ketorolac tromethamine and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients.

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Ketorolac tromethamine, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up.
2. Ketorolac tromethamine, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up.
3. Ketorolac tromethamine, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help.
7. In late pregnancy, as with other NSAIDs, ketorolac tromethamine should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash etc.) or if abnormal liver tests persist or worsen, ketorolac tromethamine should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Ketorolac is highly bound to human plasma protein (mean 99.2%). There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Warfarin, Digoxin, Salicylate, and Heparin

The in vitro binding of warfarin to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter digoxin protein binding. In vitro studies indicate that, at therapeutic concentrations of salicylate (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in unbound ketorolac plasma levels. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter ketorolac tromethamine protein binding.

In a study involving 12 adult volunteers, oral ketorolac tromethamine was coadministered with a single dose of 25 mg warfarin, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine dosed IV or IM was given with two doses of 5000 U of heparin to 11 healthy volunteers, resulting in a mean template bleeding time of 6 minutes (3.2 to 11.4 min) compared to a mean of 6.0 minutes (3.4

to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored .

The effects of warfarin and NSAIDs, in general, on GI bleeding are synergistic, such that the users of both drugs together have a risk of serious GI bleeding higher than the users of either drug alone.

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 oral ketorolac tromethamine 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.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administered concomitantly with SSRIs.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

An 18-month study in mice with oral doses of ketorolac tromethamine tablets at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg qid, based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine tablets at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1.0 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 nonsteroidal 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 tablets 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.

Labor and Delivery

The use of 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 .

Effects on Fertility

The use of ketorolac tromethamine, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of ketorolac tromethamine should be considered.

Nursing Mothers

Limited data from one published study that included 10 breastfeeding women 2-6 days postpartum showed low levels of ketorolac in breast milk and were undetectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 mg of ketorolac tromethamine, 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 400-1,000 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 healthcare provider if they note any adverse events.

Pediatric Use

Ketorolac tromethamine is not indicated for use in pediatric patients. The safety and effectiveness of ketorolac tromethamine in pediatric patients below the age of 17 have not been established.

Geriatric Use (≥65 Years of Age)

Because ketorolac tromethamine may be cleared more slowly by the elderly who are also more sensitive to the dose-related adverse effects of NSAIDs, extreme caution and reduced dosages and careful clinical monitoring must be used when treating the elderly with ketorolac tromethamine.

4.6 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 G.I. 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, hyperkinesia, 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, post operative wound hemorrhage (rarely requiring blood transfusion)

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

Postmarketing Surveillance Study

A large postmarketing observational, nonrandomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (GI) bleeding was dose-dependent. This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine.

Table 3: Incidence of Clinically Serious G.I. Bleeding as Related to Age, Total Daily Dose, and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine Injection

A. Adult Patients without History of PUB				
Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	> 120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

B. Adult Patients with History of PUB				
Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	> 120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25.0%

4.7 Overdose

Symptoms and Signs

Symptoms following acute NSAIDs 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

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 by either route is in the duration of analgesia.

5.2 Pharmacokinetic properties

Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of IV, IM and Oral Pharmacokinetics

The pharmacokinetics of ketorolac tromethamine, following IV, IM and oral doses of ketorolac tromethamine are compared in [Table 1](#). In adults, the extent of bioavailability following administration of the ORAL and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

Table 1: Table of Approximate Average Pharmacokinetic Parameters (Mean $\pm$ SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

	Oral [†]	Intramuscular*			Intravenous Bolus [‡]	
Pharmacokinetic Parameters (units)	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T _{max} ¹ (min)	44 $\pm$ 34	33 $\pm$ 21**	44 $\pm$ 29	33 $\pm$ 21**	1.1 $\pm$ 0.7**	2.9 $\pm$ 1.8
C _{max} ² (mcg/mL) [Single-dose]	0.87 $\pm$ 0.22	1.14 $\pm$ 0.32**	2.42 $\pm$ 0.68	4.55 $\pm$ 1.27**	2.47 $\pm$ 0.51**	4.65 $\pm$ 0.96
C _{max} (mcg/mL) [steady state qid]	1.05 $\pm$ 0.26**	1.56 $\pm$ 0.44**	3.11 $\pm$ 0.87**	N/A ^{††}	3.09 $\pm$ 1.17**	6.85 $\pm$ 2.61
C _{min} ³ (mcg/mL) [steady state qid]	0.29 $\pm$ 0.07**	0.47 $\pm$ 0.13**	0.93 $\pm$ 0.26**	N/A	0.61 $\pm$ 0.21**	1.04 $\pm$ 0.35
C _{avg} ⁴ (mcg/mL) [steady state qid]	0.59 $\pm$ 0.2* *	0.94 $\pm$ 0.29**	1.88 $\pm$ 0.59**	N/A	1.09 $\pm$ 0.3* *	2.17 $\pm$ 0.59

V_B^5 (L/kg)	----- 0.175±0.039 -----	0.210±0.044
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Dose metabolized = <50 % Dose excreted in feces = 6 ¹Time-to-peak plasma concentration

% Dose excreted in urine = 91 % Plasma protein binding = 99 ²Peak plasma concentration

† Derived from PO pharmacokinetic studies in 77 normal fasted volunteers ³Trough plasma concentration

* Derived from IM pharmacokinetic studies in 54 normal volunteers ⁴Average plasma concentration

‡ Derived from IV pharmacokinetic studies in 24 normal volunteers ⁵Volume of distribution

†† Not applicable because 60 mg is only recommended as a single dose

** Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data

Linear Kinetics

In adults, following administration of single ORAL, IM or IV doses of ketorolac tromethamine in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in adults, following single or multiple IM, IV or recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Distribution

The mean apparent volume (V_B) 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. 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.

Ketorolac tromethamine is excreted in human milk .

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 clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined in [Table 2](#) .The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD $\pm$ 0.4) compared with 5 hours (SD $\pm$ 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.

Accumulation

Ketorolac tromethamine administered as an IV bolus, every 6 hours for 5 days to healthy subjects (n = 13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 mcg/mL (SD $\pm$ 0.13) on Day 1 and 0.55 mcg/mL (SD $\pm$ 0.23) on Day 6. Steady state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (geriatric, pediatric, renal failure patients, or hepatic disease patients).

Kinetics in Special Populations

Geriatric Patients

Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years) (see [Table 2](#)). There was little difference in the C_{max} for the two groups (elderly, 2.52 mcg/mL $\pm$ 0.77; young, 2.99 mcg/mL $\pm$ 1.03)

Pediatric Patients

Limited information is available regarding the pharmacokinetics of dosing of ketorolac tromethamine in the pediatric population.

Following a single intravenous bolus dose of 0.5 mg/kg in 10 children 4 to 8 years old, the half-life was 5.8 ± 1.6 hours, the average clearance was 0.042 ± 0.01 L/hr/kg, the volume of distribution during the terminal phase (V_{β}) was 0.34 ± 0.12 L/kg and the volume of distribution at steady state (V_{ss}) was 0.26 ± 0.08 L/kg. The volume of distribution and clearance of ketorolac in pediatric patients was higher than those observed in adult subjects (see [Table 1](#)). There are no pharmacokinetic data available for administration of ketorolac tromethamine by the IM route in pediatric patients.

Renal Insufficiency

Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment ($r = 0.5$).

In patients with renal disease, the AUC_∞ of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC_∞-ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see WARNINGS – Renal Effects).

Hepatic Insufficiency

There was no significant difference in estimates of half-life, AUC_∞ and C_{max}, in 7 patients with liver disease compared to healthy volunteers .

Race

Pharmacokinetic differences due to race have not been identified.

Table 2: The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of Ketorolac Tromethamine (IM¹ and ORAL²) in Adult Populations.

Type of Subjects	Total Clearance [in L/h/kg] ³		Terminal Half-life [in hours]	
	IM Mean (range)	ORAL Mean (range)	IM Mean (range)	ORAL Mean (range)
Normal Subjects IM (n=54) mean age=32, range=18-60 Oral (n=77) mean age=32, range=20-60	0.023 (0.010-0.046)	0.025 (0.013-0.050)	5.3 (3.5-9.2)	5.3 (2.4-9)
Healthy Elderly Subjects IM (n=13), Oral (n=12) mean age=72, range=65-78	0.019 (0.013-0.034)	0.024 (0.018-0.034)	7 (4.7-8.6)	6.1 (4.3-7.6)
Patients with Hepatic	0.029 (0.013-0.066)	0.033 (0.019-0.051)	5.4 (2.2-6.9)	4.5 (1.6-7.6)

Dysfunction IM and Oral (n=7) mean age=51, range=43-64				
Patients with Renal Impairment IM (n=25), Oral (n=9) serum creatinine =1.9- 5.0 mg/dL mean age (IM)=54, range=35-71 mean age (Oral)=57, range=39-70	0.015 (0.005-0.043)	0.016 (0.007-0.052)	10.3 (5.9-19.2)	10.8 (3.4-18.9)
Renal Dialysis Patients IM and Oral (n=9) mean age=40, range=27-63	0.016 (0.003-0.036)	-----	13.6 (8.0-39.1)	-----

¹ Estimated from 30 mg single IM doses of ketorolac tromethamine

² Estimated from 10 mg single oral doses of ketorolac tromethamine

³ Liters/hour/kilogram

IV-Administration: In normal subjects (n=37), the total clearance of 30 mg IV-administered ketorolac tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours.

5.3 Preclinical safety data

Toxicology

In repeat-dose toxicology studies in animals, hepatic effects (Kupffer-cell hypertrophy/hyperplasia, mononuclear cell infiltrates and bile duct hyperplasia) and adrenal gland effects (changes in cytoplasmic vacuolation and adrenal cortical hypertrophy/hyperplasia) were observed at exposures similar or slightly higher than the clinical AUC exposure. In dogs, bone marrow hypocellularity with correlating clinical pathology changes were observed at exposures 9-fold the clinical AUC exposure. None of these effects have been observed in humans.

Carcinogenesis and mutagenesis

Daclatasvir was not carcinogenic in mice or in rats at exposures 8-fold or 4-fold, respectively, the clinical AUC exposure. No evidence of mutagenic or clastogenic activity was observed in *in vitro* mutagenesis (Ames) tests, mammalian mutation assays in Chinese hamster ovary cells, or in an *in vivo* oral micronucleus study in rats.

Fertility

Daclatasvir had no effects on fertility in female rats at any dose tested. The highest AUC value in unaffected females was 18-fold the clinical AUC exposure. In male rats, effects on reproductive endpoints were limited to reduced prostate/seminal vesicle weights, and minimally increased dysmorphic sperm at 200 mg/kg/day; however, neither finding adversely affected fertility or the number of viable conceptuses sired. The AUC associated with this dose in males is 19-fold the clinical AUC exposure.

Embryo-foetal development

Daclatasvir is embryotoxic and teratogenic in rats and rabbits at exposures at or above 4-fold (rat) and 16-fold (rabbit) the clinical AUC exposure. Developmental toxicity consisted of increased embryofoetal lethality, reduced foetal body weights and increased incidence of foetal malformations and variations. In rats, malformations mainly affected the brain, skull, eyes, ears, nose, lip, palate or limbs and in rabbits, the ribs and cardiovascular area. Maternal toxicity including mortality, abortions, adverse clinical signs, decreases in body weight and

food consumption was noted in both species at exposures 25-fold (rat) and 72-fold (rabbit) the clinical AUC exposure.

In a study of pre- and postnatal development in rats, there was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day, associated with AUC values 2-fold the clinical AUC exposure. At the highest dose (100 mg/kg/day), maternal toxicity included mortality and dystocia; developmental toxicity included slight reductions in offspring viability in the peri- and neonatal periods; and reductions in birth weight that persisted into adulthood. The AUC value associated with this dose is 4-fold the clinical AUC exposure.

Excretion into milk

Daclatasvir was excreted into the milk of lactating rats with concentrations 1.7- to 2-fold maternal plasma levels.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride USP, Citric acid monohydrate USP, Ethanol absolute USP, Sodium hydroxide USP/NF, Hydrochloric acid USP/NF, Water for injection IP, USP & Ph.Eur

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months (2 years)

6.4 Special precautions for storage

Store below 30°C and protection from light.

6.5 Nature and contents of container

Primary pack: 21's count (2R, 2 mL Amber color Tubular glass vial, USP Type--I with 13 mm Serum grey bromo butyl rubber stopper (RS) and 13 mm orange color flip off seal).

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

7.1 Name and Address of Manufacturer

Name: Aspiro Pharma Limited
Business Address: Survey No. 321, Biotech Park, Phase III,,
Karkapatla village, Markook Mandal,
Siddipet (Dist) – 502281,
Telangana.
Country: INDIA
Phone: Tel +91 9959644022, 9959644077

7.2 Name and Address of Principal

Name: Aspiro Pharma Limited
Business Address: Survey No. 321, Biotech Park, Phase III,,
Karkapatla village, Markook Mandal,
Siddipet (Dist) – 502281,
Telangana.
Country: INDIA
Phone: Tel +91 9959644022, 9959644077

8. REGISTRATION NUMBER

Not applicable

9. DATE OF PUBLICATION OF THIS PACKAGE INSERT

Not applicable