PROFESSIONAL INFORMATION FOR OFLAECT 15/30/60 INJECTION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

OFLAECT 15 INJECTION

OFLAECT 30 INJECTION

OFLAECT 60 INJECTION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OFLAECT 15 INJECTION: Each vial mL contains 15 mg ketorolac tromethamine (15 mg/mL).

OFLAECT 30 INJECTION: Each vial mL contains 30 mg ketorolac tromethamine (30 mg/mL).

OFLAECT 60 INJECTION: Each vial mL contains 30 mg ketorolac tromethamine (60 mg/2 mL).

OFLAECT INJECTION is sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A clear and slight yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OFLAECT INJECTION is indicated for the short-term management of moderate post-operative pain. It is not indicated for chronic painful conditions.

4.2 Posology and method of administration

Posology

In adults, **OFLAECT INJECTION** may be used as a single or multiple dose *IM* or bolus *IV* injection.

OFLAECT INJECTION may be used for short-term *IV* or *IM* use, not exceeding 2 days.

The lowest effective dose should be given. Opiate analgesics (e.g. morphine, pethidine) may be used concomitantly if further pain relief is required. When used in association with **OFLAECT INJECTION**, the daily dose of morphine required is less than that normally required following major surgery. However, opioid side effects should still be considered, especially in day-case surgery.

Hypovolaemia should be corrected prior to the administration of **OFLAECT INJECTION**.

a) Single dose treatment:

IM dosing

Patients < 65 years of age: One dose of 10 – 60 mg according to the severity of the pain.

Patients ≥ 65 years of age, or mildly renally impaired patients: One dose of 10 – 30 mg.

IV dosing

Patients < 65 years of age: One dose of 10 – 30 mg.

Patients ≥ 65 years of age, or mildly renally impaired patients: One dose of 10 – 15 mg.

b) Multiple-dose treatment (*IV* or *IM*):

Dosage should be adjusted according to the severity of the pain and the patient response. Note that the maximum combined duration of use of multiple bolus *IM* or *IV* doses of **OFLAECT INJECTION** is not to exceed 2 days.

Patients < 65 years of age

The maximum daily dose should not exceed 90 mg.

IM dosing

The recommended usual initial dose of **OFLAECT INJECTION** is 10 – 30 mg, followed by 10 – 30 mg every 4

– 6 hours as required, up to a maximum daily dose of 90 mg.

IV dosing

IV bolus: 10 – 30 mg initial dose, followed by 10 – 30 mg every 6 hours as required, up to a maximum daily dose of 90 mg.

Patients ≥ 65 years of age, or renally impaired patients

The maximum daily dose should not exceed 60 mg.

IM dosing

The recommended dose is 10 – 15 mg every 4 – 6 hours as required up to a maximum daily dose of 60 mg.

IV dosing

IV bolus: 10 – 15 mg every 6 hours as required, up to maximum daily dose of 60 mg.

Transition from OFLAECT INJECTION to ketorolac tablets

On the day of transition to the oral formulation, a total combined daily dose of all forms of ketorolac should not exceed 90 mg for patients ≤ 65 years of age and 60 mg for patients > 65 years of age, renally impaired patients and patients weighing less than 50 kg. The total oral dose should not exceed 40 mg on the day the change of formulation is made.

Special populations

Elderly patients (≥ 65 years of age):

Ketorolac tromethamine may be cleared more slowly by the elderly who are also more sensitive to the adverse effects of NSAIDs, therefore extra caution and reduced dosages must be used when treating the elderly (see **sections 4.4** and **4.8**).

Patients with renal impairment:

OFLAECT INJECTION and its metabolites are eliminated primarily via the kidneys, which, in patients with

reduced creatinine clearance, will result in diminished plasma clearance of the medicine. **OFLAECT INJECTION** is contraindicated in moderate or severe renal impairment (serum creatinine > 442 µmol/L). **OFLAECT INJECTION** should be used with caution in patients with lesser renal impairment (serum creatinine 170 – 442 µmol/L). Such patients should receive a reduced dose of **OFLAECT INJECTION** and their renal status should be closely monitored. It is recommended that the daily dose be reduced by half; a total daily dose of 60 mg should not be exceeded. Dialysis does not significantly clear ketorolac from the bloodstream.

Paediatric population

The use of **OFLAECT INJECTION** in children under 16 years of age is not recommended.

Method of administration

OFLAECT INJECTION is administered as intramuscular or bolus intravenous injection. Do not use if particulate matter is present.

Bolus doses should 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 approximately 30 minutes with maximum effect within 1 – 2 hours after dosing. The median duration of analgesia is generally 4 – 6 hours.

Pharmaceutical compatibility

OFLAECT INJECTION is compatible with normal saline, 5 % dextrose, ringer's,

lactated ringer's or plasmalyte solutions.

4.3 Contraindications

- Patients with hypersensitivity to ketorolac tromethamine, other NSAIDs or any other component listed in section 6.1, and those patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients). Such reactions have included asthma, rhinitis, angioedema or urticaria.
- 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.

- Patients on anti-coagulation therapy including prophylactic low-dose heparin or low molecular weight heparins or heparinoids.
- Haemorrhagic diatheses, including coagulation disorders.
- **OFLAECT INJECTION** inhibits platelet function and is therefore contraindicated in patients with confirmed or suspected cerebrovascular bleeding, patients who have had operations with a high risk of haemorrhage or incomplete haemostasis, and those at high risk of bleeding.
- **OFLAECT INJECTION** is contraindicated in patients with severe heart failure, hepatic failure and renal failure (see **section 4.4**).
- In patients with moderate or severe renal impairment (serum creatinine > 442 µmol/L) or in patients at risk of renal failure due to volume depletion or dehydration.
- During pregnancy, labour, delivery or lactation (see **section 4.6**).
- Safety and efficacy in children under 16 years of age have not been established. **OFLAECT INJECTION** in children is not recommended.
- As prophylactic analgesics before surgery, due to inhibition of platelet aggregation, and also intra-operatively, because of increased risk of bleeding.
- **OFLAECT INJECTION** is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.
- The combination of **OFLAECT INJECTION** and oxypentifylline is contraindicated.
- **OFLAECT INJECTION** is contraindicated in patients currently receiving ASA or other NSAIDS (including cyclooxygenase-2 selective inhibitors).
- Concurrent treatment with ketorolac and probenecid or lithium salts is contraindicated.
- Ketorolac is contraindicated in patients with the complete or partial syndrome of nasal polyps, angioedema or bronchospasm.

4.4 Special warnings and precautions for use

Epidemiological evidence suggests that ketorolac may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially when used outside the licensed indications and/or for prolonged periods (see sections 4.1, 4.2 and 4.3).

Medical practitioners should be aware that in some patients pain relief may not occur until upwards of 30

minutes after *IV* or *IM* administration.

The use of Ketorolac with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see **sections 4.2** and **GI and cardiovascular risks below**).

Gastrointestinal ulceration, bleeding and perforation

Gastrointestinal mucosal injury may occur. Serious gastrointestinal toxicity, including gastrointestinal irritation, bleeding, ulceration or perforation, can occur at any time with, or without, previous symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding.

Parenterally administered **OFLAECT INJECTION** suggests that there may be a greater risk of gastrointestinal ulceration, bleeding and perforation in the elderly and debilitated patients. Most spontaneous reports of fatal gastrointestinal events are in this population.

The incidence and severity of gastrointestinal complications increase with increasing dose and duration of treatment with **OFLAECT INJECTION**. The risk of clinically serious gastrointestinal bleeding is dose dependent. This is particularly true in elderly patients who receive an average daily dose greater than 60 mg/day of **OFLAECT INJECTION**. A history of peptic ulcer disease increases the possibility of developing serious gastrointestinal complications during **OFLAECT INJECTION** therapy.

Use in patients with impaired renal function

OFLAECT INJECTION 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.

In patients on renal dialysis, ketorolac clearance was reduced to approximately half the normal rate and terminal half-life increased approximately three-fold.

Caution should be observed as renal toxicity has been seen with **OFLAECT INJECTION** and other NSAIDs in patients with conditions leading to a reduction in blood volume and/or renal blood flow where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration

of **OFLAECT INJECTION** or other NSAIDs may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal decomposition or renal failure. Patients at greatest risk of this reaction are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of **OFLAECT INJECTION** or other NSAID therapy is usually followed by recovery to the pre-treatment state.

Anaphylactic reactions

Anaphylactic reactions, including, but not limited to, anaphylaxis, bronchospasm, flushing, rash, hypotension, laryngeal oedema and angioedema may occur in patients, with or without a history of hypersensitivity to aspirin, other NSAIDs or **OFLAECT INJECTION**. These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma) and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Therefore, **OFLAECT INJECTION** should be used with caution in patients with a history of asthma and in patients with the complete or partial syndrome of nasal polyps, angioedema and bronchospasm.

Haematological effects

OFLAECT INJECTION inhibits platelet aggregation, reduces thromboxane concentrations and prolongs bleeding time. Platelet function returns to normal within 24 to 48 hours after **OFLAECT INJECTION** is discontinued. The use of **OFLAECT INJECTION** in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. The concurrent use of **OFLAECT INJECTION** and therapy that affects haemostasis, including therapeutic doses of anticoagulation therapy (warfarin), prophylactic low dose heparin (2 500 – 5 000 units 12-hourly) and dextrans, may be associated with an increased risk of bleeding (see **section 4.3**).

Increased post-operative wound haemorrhage has been reported in association with the immediate peri-operative use of **OFLAECT INJECTION**. Therefore, **OFLAECT INJECTION** should not be used in patients who have had operations with a high risk of haemorrhage or incomplete haemostasis.

Caution should be used where strict haemostasis is critical, e.g. in cosmetic or day-case surgery. Haematoma and other signs of wound haemorrhage and epistaxis have been reported with the use of **OFLAECT INJECTION**. Medical practitioners should be aware of the pharmacological similarity of **OFLAECT INJECTION**

to other NSAIDs, medicines that inhibit cyclo-oxygenase and the risk of bleeding, particularly in the elderly.

Elderly patients

Elderly patients may be at a greater risk of experiencing undesirable effects than younger patients. In elderly patients the terminal plasma half-life of ketorolac is prolonged and plasma clearance may be reduced. The lower end of the dosage range is recommended.

Fluid retention and oedema

Fluid retention, hypertension and oedema have been reported with the use of **OFLAECT INJECTION** and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.

Hepatic effects

Elevations of one or more liver tests may occur. These abnormalities may be transient, may remain unchanged, or may progress with continued therapy. **OFLAECT INJECTION** should be discontinued if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs (see **section 4.8**). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (including anaphylaxis, angioedema and drug
rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity
syndrome), have been reported in patients receiving cyclo-oxygenase enzyme
inhibitors such as OFLAECT INJECTION, (see section 4.8). **OFLAECT INJECTION** should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see **section 4.8**).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Use of coxibs and some NSAIDs (particularly at high doses) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although ketorolac has not shown to increase thrombotic events such as myocardial infarction, there are insufficient data to exclude such a risk for Ketorolac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Ketorolac after careful consideration. Similar consideration should be made before initiating treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Paediatric population

Safety and efficacy in children (less than 16 years of age) have not been established. Therefore the use of **OFLAECT INJECTION** in children is not recommended.

Excipients with known effect:

Ethanol absolute: The small amount of alcohol in this medicine will not have any noticeable effects.

Sodium chloride: This medicine contains less than 1 mmol sodium (23 mg) per <dosage unit><unit volume>, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicine and other forms of interaction

OFLAECT INJECTION should not be used with other NSAIDs because of the potential for additive side effects.

Because of an increased tendency to bleeding when oxpentifylline is administered concurrently, this combination should be avoided (see **section 4.3**).

Caution is advised when probenecid is administered concurrently, as alterations in the pharmacokinetics of **OFLAECT INJECTION** have been reported with this combination. A decreased plasma clearance and volume of distribution, increased plasma concentrations and increased half-life of ketorolac (as in **OFLAECT INJECTION**) have been reported.

Caution is advised when methotrexate is administered concurrently, since some prostaglandin synthesis-inhibiting medicines have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity.

Inhibition of renal lithium clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis-inhibiting medicines. Cases of increased lithium plasma concentrations during **OFLAECT INJECTION** therapy have been reported.

OFLAECT INJECTION did not alter digoxin protein binding. Salicylate at concentrations of 300 µg/mL and above reduces the protein binding by approximately 99,2 – 97,5 %, representing a potential twofold increase in unbound ketorolac (as in **OFLAECT INJECTION**) plasma concentrations. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, paracetamol, phenytoin and tolbutamide did not alter **OFLAECT INJECTION** protein binding.

OFLAECT INJECTION reduces the diuretic response to furosemide in normovolaemic healthy volunteers by approximately 20 %, so particular care should be exercised in patients with cardiac decompensation.

There is an increased risk of renal impairment when **OFLAECT INJECTION** is administered concurrently with ACE inhibitors, particularly in volume depleted patients.

OFLAECT INJECTION should not be used with other ASA or other NSAIDs including cyclooxygenase-2 selective inhibitors as the risk of inducing serious NSAID related adverse events may be increased (see **section 4.3**).

Ketorolac inhibits platelet aggregation, reduces thromboxane concentrations and prolongs bleeding time. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24-48 hours after ketorolac is discontinued.

OFLAECT INJECTION is contraindicated in combination with anti-coagulants, such as warfarin since co-administration of NSAIDs and anti-coagulants may cause an enhanced anti-coagulant effect (see **section 4.3**).

NSAIDs should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding (see **section 4.4**).

There is an increased risk of gastrointestinal bleeding (see **section 4.4**) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.

Caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function

(e.g. dehydrated patients or elderly patients) when ACE inhibitors and/or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately titrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

Ketorolac has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

NSAIDs given with zidovudine increase the risk of haematological toxicity. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Abuse and dependence:

OFLAECT INJECTION is devoid of addictive potential. No withdrawal symptoms have been observed following abrupt discontinuation of **OFLAECT INJECTION**.

4.6 Fertility, pregnancy and lactation

Pregnancy

OFLAECT INJECTION is contraindicated during pregnancy and lactation (see **section 4.3**).

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin

synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period

Second and Third trimester.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

Breastfeeding

Ketorolac crosses the placenta and has been detected in human milk at low concentrations.

Fertility

The use of **OFLAECT INJECTION**, as with any medicine 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 fertility, withdrawal of **OFLAECT INJECTION** should be considered.

4.7 Effects on ability to drive and use machines

Patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of **OFLAECT INJECTION**. If patients experience these, or other similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 Undesirable effects

b) Tabulated list of adverse reactions

Blood and lymphatic system disorders

Frequent: Purpura.

Less frequent: Thrombocytopenia, post-operative wound haemorrhage, epistaxis.

Frequency unknown: Haematoma, increased bleeding time.

Metabolism and nutrition disorders

Less frequent: Excessive thirst.

Psychiatric disorders

Less frequent: Depression, hallucinations, psychotic reactions.

Frequency unknown: Nervousness, abnormal thinking, euphoria, inability to concentrate, insomnia, abnormal dreams, anxiety.

Nervous system disorders

Frequent: Drowsiness, dizziness, headache, sweating.

Less frequent: Hyperkinesia, convulsions, aseptic meningitis.

Frequency unknown: Paraesthesia, vertigo.

Eye disorders

Less frequent: Abnormal vision.

Ear and labyrinth disorders

Less frequent: Tinnitus, hearing loss.

Cardiac disorders

Frequency unknown: Bradycardia, palpitations, chest pain.

Vascular disorders

Frequent: Hypertension.

Less frequent: Hypotension.

Frequency unknown: Flushing, pallor.

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea, asthma, pulmonary oedema.

Gastrointestinal disorders

Frequent: Nausea, dyspepsia, gastrointestinal pain, abdominal discomfort, diarrhoea, constipation, flatulence, fullness, stomatitis, vomiting.

Less frequent: Melaena, peptic ulcer, rectal bleeding, haemorrhage, perforation, pancreatitis.

Frequency unknown: Dry mouth, gastritis, eructation, esophagitis, abnormal taste.

Hepato-biliary disorders

Less frequent: Hepatitis, cholestatic jaundice.

Frequency unknown: Abnormal liver function tests, liver failure.

Skin and subcutaneous tissue disorders

Less frequent: Pruritus, urticaria, Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash.

Musculoskeletal and connective tissue disorders

Frequency unknown: Myalgia.

Renal and urinary disorders

Less frequent: Increased urinary frequency, oliguria, acute renal failure, haemolytic uraemic syndrome, flank pain (with or without haematuria), interstitial nephritis. Signs of renal impairment, such as, but not limited to,

elevations of creatinine and potassium, can occur after one dose of **OFLAECT INJECTION**.

Frequency unknown: Hyponatraemia, hyperkalaemia, raised serum urea and creatinine, urinary retention, nephrotic syndrome.

General disorders and administration site conditions

Frequent: Oedema, weight gain, injection site reactions.

Less frequent: Fever.

Frequency unknown: Asthenia.

POST MARKETING

Blood and lymphatic system disorders: Neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Immune system disorders: anaphylaxis, anaphylactoid reactions, anaphylactoid reactions like anaphylaxis, may have a fatal outcome, hypersensitivity reactions such as bronchospasm flushing, rash, hypotension, laryngeal oedema.

These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma and nasal polyps).

Metabolism and nutrition disorders: anorexia.

Psychiatric disorders: Confusion and stimulation have been observed.

Eye Disorders: visual disturbances, optic neuritis.

Ear Disorders: vertigo.

Cardiac Disorders: cardiac failure.

Vascular disorders: haematoma, postoperative wound haemorrhage.

Reproductive System and Breast Disorders: female infertility.

Respiratory, Thoracic and Mediastinal Disorders: epistaxis

Gastro-intestinal disorders: ulcers, sometimes fatal, haematemesis, ulcerative stomatitis, gastrointestinal ulceration, exacerbation of colitis and Crohn's disease.

Infection: meningitis aseptic. (especially in patients with existing auto-immune disorders, such as systemic

lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation.

Skin and Subcutaneous Tissue Disorders: angioedema, sweating, toxic epidermal necrolysis (very rare). Additionally erythema multiforme and skin photosensitivity.

Musculoskeletal and Connective Tissue Disorders: functional disorder.

General Disorders and Administration Site Condition: excessive thirst, and pain, chest pain.

Additionally, malaise, fatigue has been observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com

4.9 Overdose

Doses of 360 mg given intramuscularly over an 8-hour interval for five consecutive days have caused abdominal pain, nausea, vomiting, hyperventilation, erosive gastritis, renal dysfunction and peptic ulcers which have healed after discontinuation of dosing.

OFLAECT INJECTION is not appreciably cleared by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.7 Anti-pyretic and anti-inflammatory analgesics

ATC code: M01AB15.

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, acetic acid derivatives and related substances.

Ketorolac tromethamine is an analgesic medicine of the nonsteroidal anti-inflammatory class (NSAIDs), with

analgesic, anti-inflammatory and antipyretic properties. It demonstrates a minimal anti-inflammatory effect at its analgesic dose. Its mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis. It is considered a peripherally acting analgesic and has no known effects on opiate receptors.

5.2 Pharmacokinetic properties

Absorption:

IM administration

Ketorolac is completely absorbed following *IM* administration with a mean peak plasma concentration of 2,2 – 3,0 µg/mL occurring on average 50 minutes after a single 30 mg dose.

Bolus administration

IV administration of a single 10 mg dose of ketorolac results in a mean peak plasma concentration of 2,4 µg/mL occurring on average 5,4 minutes after dosing.

Distribution:

The pharmacokinetics of ketorolac in humans, following single or multiple *IM* or *IV* doses, are linear. Steady-state plasma levels are approached after the fourth dose when ketorolac is administered as an *IV* bolus every 6 hours, for one day.

More than 99 % of the ketorolac in plasma is protein-bound, with a mean volume of distribution of 0,15 L/kg following *IV* and *IM* administration of single 10 mg doses to young, healthy adult volunteers.

Nearly all the material that is circulating in plasma related to the active ingredient is ketorolac or the pharmacologically inactive p-hydroxyketorolac.

Ketorolac crosses the placenta to the extent of approximately 10 %. Ketorolac has been detected in human milk at low concentrations (see **section 4.3**).

Biotransformation:

Ketorolac is largely metabolised in the liver. The major metabolic pathway of ketorolac in humans is glucuronic acid conjugation. P-hydroxylation is an additional major pathway.

Elimination:

Ketorolac and its metabolites are mainly eliminated renally. 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 faeces. The terminal plasma half-life averages 5,3 hours, ranging from 2,4 – 9,2 hours, and the total plasma clearance averages 0,023 L/h/kg, in young healthy volunteers.

Characteristics in specific groups of patients

Elderly patients

In the elderly, the terminal plasma half-life of ketorolac is prolonged to an average of 7 hours, ranging from 4,3 – 8,6 hours, compared to young, healthy volunteers. The total plasma clearance may be reduced, on average to 0,019 L/h/kg.

Renal impairment

Elimination of ketorolac is significantly decreased in patients with renal impairment as reflected by a prolonged plasma half-life and reduced plasma clearance, when compared to young healthy volunteers. The rate of elimination is reduced, roughly proportional to the degree of renal impairment, except for patients who are severely renally impaired, in whom there is a higher plasma clearance of ketorolac than estimated from the degree of renal impairment alone.

Hepatic impairment

Patients with impaired hepatic function have significant prolongation of T_{max} and terminal plasma half-life compared to young healthy volunteers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Ethanol absolute

Sodium chloride

Water for injection

6.2 Incompatibilities

OFLAECT INJECTION should not be mixed in small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride, as precipitation will occur.

6.3 Shelf life

24 months. After opening **OFLAECT INJECTION** must be used immediately.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the vial in the outer carton until required for use.

This medicine does not require any special storage conditions.

For single use only. Discard any unused portion.

6.5 Nature and contents of container

OFLAECT 15 INJECTION: 2 mL Type-I, round amber colored tubular glass vial with 13 mm grey colored serum bromobutyl rubber stopper and 13 mm yellow flip off aluminium seal, packed in an outer carton.

Pack size: 5 vials.

OFLAECT 30 INJECTION: 2 mL Type-I, round amber colored tubular glass vial with 13 mm grey colored serum bromobutyl rubber stopper and 13 mm orange flip off aluminium seal, packed in an outer carton.

Pack size: 5 or 10 vials.

OFLAECT 60 INJECTION: 2 mL Type-I, round amber colored tubular glass vial with 13 mm grey colored serum bromobutyl rubber stopper and 13 mm dark blue flip off aluminium seal, packed in an outer carton.

Pack size: 5 or 10 vials.

Not all pack sizes may be marketed.

Vials are kept in an outer carton until required for use.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall corporate campus,

Building no. 2, first floor,

74 waterfall drive,

Midrand 2066

Tell: 0126441220.

8 REGISTRATION NUMBER(S)

OFLAECT 15 INJECTION: 54/2.7/0286.

OFLAECT 30 INJECTION: 54/2.7/0287.

OFLAECT 60 INJECTION: 54/2.7/0288.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

08 August 2023

10 DATE OF REVISION OF THE TEXT

08 August 2023