Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BEDORAL® 30 (INJECTION)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 30 mg of ketorolac tromethamine.

3. PHARMACEUTICAL FORM

Solution for injection

A clear, colourless solution, free from visible particles and fibres.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BEDORAL® 30 is used in the short-term management of moderate post-operative pain.

4.2 Posology and method of administration

Children: BEDORAL® 30 injection is not recommended for use in children under 16 years of age.

Adults: BEDORAL® 30 injection may be used as a single or multiple dose *IM* or bolus *IV* injection, or *IV* infusion.

BEDORAL® 30 injection may be used for short-term *IV* or *IM* use, not exceeding two days.

The maximum duration for use of the *IV* infusion, is not to exceed 24 hours. The lowest effective dose should be given. If further pain relief is required, opiate analgesics (e.g. morphine, pethidine) may be used concomitantly.

When used in association with **BEDORAL® 30**, 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. Hypovolemia should be corrected prior to the administration of **BEDORAL® 30**. **BEDORAL® 30** infusion should be used only in patients with adequate fluid and electrolyte balance. 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.

1) 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.

2) 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 **BEDORAL® 30** 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 **BEDORAL® 30** 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. *Continuous IV infusion:* 30 mg initial dose, followed by continuous infusion at a rate of up to 5 mg/h for up to 24 hours, 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. I*M 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 a maximum daily dose of 60 mg. *Continuous IV* infusion is not recommended in this population as experience is limited.

Transition from BEDORAL® 30 injection to ketorolac tablets:

On the day of transition to the oral formulation, a total combined daily dose of all forms of **BEDORAL® 30** 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.

Elderly patients (≥ 65 years of age):

BEDORAL® 30 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 Section 4.4 and 4.8).

Patients with renal impairment :

BEDORAL® 30 and its metabolites are eliminated primarily via the kidneys, which, in patients with reduced creatinine clearance, will result in diminished plasma clearance of the drug. **BEDORAL® 30** is contra-indicated in moderate or severe renal impairment

(serum creatinine > 442 µmol/l). **BEDORAL® 30** 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 **BEDORAL® 30** 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 **BEDORAL® 30** from the blood stream.

Pharmaceutical compatibility:

BEDORAL® 30 injection is compatible with 0,9 % sodium chloride solution, 5 % dextrose, Ringer's lactate, plasmalyte solutions. **BEDORAL® 30** should not be mixed in small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride, as precipitation of **BEDORAL® 30** will occur. When mixed together in *IV* solutions contained in standard bottles or bag administration sets, it is compatible with aminophylline, lidocaine hydrochloride, morphine sulphate, meperidine hydrochloride, dopamine hydrochloride, regular human insulin and heparin sodium.

DO NOT USE if particulate matter is present.

4.3 Contraindications

Hypersensitivity to ketorolac tromethamine or other NSAIDs and those patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients).

In patients with recent gastrointestinal bleeding or perforation, in patients with active peptic ulcer disease and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Haemorrhagic diatheses, including coagulation disorders. Patients on anti-

coagulation therapy including prophylactic low-dose heparin or low molecular weight heparins or heparinoids.

BEDORAL® 30 inhibits platelet function and is therefore contra-indicated in patients with suspected or confirmed cerebrovascular bleeding, patients who have had operations with a high risk of haemorrhage or incomplete haemostasis and those at high risk of bleeding.

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.

BEDORAL® 30 is contra-indicated during pregnancy and lactation. (See: Pregnancy and Lactation).

Safety and efficacy in children under 16 years of age have not been established. As prophylactic analgesics before surgery, due to inhibition of platelet aggregation, and also intra-operatively, because of increased risk of bleeding.

BEDORAL® 30 is contra-indicated for neuraxial (epidural or intrathecal) administration.

The combination of **BEDORAL® 30** and oxpentifylline is contra-indicated.

Pregnancy and lactation: The use of **BEDORAL® 30** around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. (see Section 4.4 and 4.6).

4.4 Special warnings and precautions for use

Gastrointestinal ulceration, bleeding and perforation:

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

gastrointestinal ulceration, bleeding and perforation in debilitated patients and in the elderly. Most spontaneous reports of fatal GI events are in this population.

The severity and incidence of gastrointestinal complications increases with increasing dose and duration of treatment with **BEDORAL® 30.** 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 **BEDORAL® 30.**

Use in Patients with impaired renal function:

BEDORAL® 30 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, **BEDORAL® 30** 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 **BEDORAL® 30** 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 **BEDORAL® 30** or other NSAIDs may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal decomposition or renal failure. Patients at greater risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of **BEDORAL® 30** 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 **BEDORAL® 30**. 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, **BEDORAL® 30** 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.

BEDORAL® 30 should not be used for chronic painful conditions.

Abuse and dependence :

BEDORAL® 30 is devoid of addictive potential. Following abrupt discontinuation of **BEDORAL® 30**, no withdrawal symptoms have been observed.

Paediatric Use:

Safety and efficacy in children (less than 16 years of age) have not been established. Therefore the use of **BEDORAL® 30** in children is not recommended.

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 **BEDORAL® 30** is prolonged and plasma clearance may be reduced. The lower end of the dosage range is recommended.

Hematological effects:

BEDORAL® 30 inhibits platelet aggregation, reduces thromboxane concentrations and prolongs bleeding time. Platelet function returns to normal within 24 to 48 hours after **BEDORAL® 30** is discontinued. The use of **BEDORAL® 30** in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. The concurrent use of **BEDORAL® 30** and therapy that affects haemostasis, including therapeutic doses of anticoagulation therapy (warfarin), prophylactic low dose heparin (2500-5000 units 12-hourly) and dextrans, may be associated with an increased risk of bleeding (see Contra-indications). Increased post-operative wound haemorrhage has been reported in association with the immediate peri-operative use of **BEDORAL® 30** injection. Therefore, **BEDORAL® 30** 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 **BEDORAL® 30**. Physicians should be aware of the pharmacological similarity of **BEDORAL® 30** to other non-steroidal anti-inflammatory agents, drugs that inhibit cyclo-oxygenase and the risk of bleeding, particularly in the elderly.

Fluid retention and oedema:

Fluid retention, hypertension and oedema have been reported with the use of **BEDORAL® 30** 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. **BEDORAL® 30** should be discontinued if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur.

Neonatal renal impairment and Oligohydramnios:

The use of **BEDORAL® 30** around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible.

Additionally it should be avoided at 30 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs (see Section 4.3. 4.4 and 4.6).

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **BEDORAL® 30.** Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling.

Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection.

Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue **BEDORAL® 30** and evaluate the patient immediately.

4.5 Interaction with other medicines and other forms of interaction

Because of the potential for additive side-effects, **BEDORAL® 30** should not be used with other NSAIDs.

There is an increased tendency to bleeding when oxpentifylline is administered concurrently and this combination should be avoided. 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 drugs.

Cases of increased lithium plasma concentrations during **BEDORAL® 30** therapy have been reported.

There is an increased risk of renal impairment when **BEDORAL® 30** is administered concurrently with ACE inhibitors particularly in volume depleted patients.

BEDORAL® 30 does not alter digoxin protein binding.

Salicylate, at therapeutic concentrations of 300 microgram/ml and above, reduces the protein binding of **BEDORAL® 30** approximately 99,2 – 97,5 %, representing a two-fold increase in unbound **BEDORAL® 30** plasma concentrations. Therapeutic concentrations of warfarin, naproxen, ibuprofen, piroxicam, acetaminophen, phenytoin and tolbutamide does not alter **BEDORAL® 30** protein binding. **BEDORAL® 30** should not be given to

patients already receiving anticoagulants or to those who will require prophylactic anticoagulant therapy, including low dose heparin. **BEDORAL® 30** injection reduces the diuretic response to furosemide in normovolaemic healthy subjects by approximately 20 %, so particular care should be exercised in patients with cardiac decompensation.

4.6 Fertility, pregnancy and lactation

BEDORAL® 30 is contraindicated during pregnancy and lactation.

During pregnancy, labour, delivery or lactation, because of its prostaglandin synthesis inhibiting effect, it may adversely affect foetal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage.

Pregnant women should not use **BEDORAL® 30** at 20 weeks or later unless specifically advised to do so by a health care professional because it may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Additionally it should be avoided at 30 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus (see Section 4.3, 4.4 and 4.6).

4.7 Effects on ability to drive and use machines

Patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of **BEDORAL® 30.** If patients experience these, or other similar undesirable effects, caution should be exercised in carrying out activities that require alertness.

4.8 Undesirable effects

System Organ Class	Frequent	Less frequent	Frequency Unknown
Blood and lymphatic system disorders	Purpura	Thrombocytopaenia, post-operative wound haemorrhage, epistaxis	Haematoma, increased bleeding time
Psychiatric disorders		Depression, hallucinations, psychotic reactions	Nervousness, abnormal thinking, euphoria, Inability to concentrate, insomnia, abnormal dreams and anxiety.
Nervous system disorders	Headache, Drowsiness, dizziness	Convulsions, aseptic meningitis	
Eye disorders		Abnormal vision	
Ear and labyrinth disorders		Tinnitus, hearing loss	Vertigo
Cardiac disorders	Hypertension	Hypotension	Flushing, bradycardia, pallor, palpitations, chest pain.
Respiratory, thoracic and mediastinal disorders		Dyspnoea, asthma, pulmonary oedema.	

Gastrointestinal disorders	Nausea, dyspepsia, gastrointestinal pain, abdominal discomfort, diarrhoea, constipation, flatulence, fullness, stomatitis, vomiting	Melaena, peptic ulcer, rectal bleeding, hemorrhage, perforation, pancreatitis.	Gastritis, eructation, esophagitis
Hepato-biliary disorders		Hepatitis, cholestatic jaundice.	Abnormal liver function tests, liver failure.
Skin and subcutaneous tissue disorders		Pruritus, urticaria, Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash.	Drug reaction with Eosinophillia and Systemic Symptoms (DRESS) [see section 4.4]
Musculoskeletal, connective tissue and bone disorders		Hyperkinesia	Paraesthesia and myalgia
Renal and urinary disorders		Increased urinary frequency, oliguria, acute renal failure, haemolytic uraemic syndrome, flank pain (with or without haematuria), interstitial nephritis. Signs of renal impairment, leading to elevations of creatinine and potassium, can occur after one dose of **BEDORAL® 30.**	Hyponatraemia, hyperkalaemia, raised serum urea and creatinine, urinary retention, nephritic syndrome.

General disorders and administrative site conditions	sweating, excessive thirst, injection site reactions, oedema, weight gain	Fever	Dry mouth, abnormal taste, asthenia

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 to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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. **BEDORAL® 30** is not appreciably cleared by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 2.7 Anti-pyretic or anti-pyretic and anti-inflammatory analgesics.

ATC code M01AB15

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

Ketorolac tromethamine is an analgesic agent of the non-steroidal anti-inflammatory class (NSAID), with analgesic, anti-inflammatory and antipyretic properties. Minimal anti-

inflammatory effect is demonstrated at its analgesic dose.Ketorolac inhibits the cyclo-oxygenase enzyme system and hence prostaglandin synthesis.

Ketorolac has no known effects on opiate receptors and is considered a peripherally acting analgesic.

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 an average of 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 an average of 5,4 minutes after dosing.

***IV* infusion:** In young, healthy adult volunteers, mean peak plasma concentrations occur about 5 minutes after an initial loading dose of 30 mg *IV* has been completed. Continuous infusion at 5 mg/hour thereafter, maintains plasma concentrations in the same range as those achieved following *IM* administration of a single 30 mg dose every 6 hours.

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. Ketorolac is over 99 % bound to plasma protein, 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 drug-related material circulating in plasma is ketorolac or the pharmacologically

inactive p-hydroxyketorolac. Approximately 10 % of ketorolac crosses the placenta. Low concentrations of ketorolac has been detected in breast milk.

Metabolism:

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

Elimination:

The principal route of elimination of ketorolac and it's 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 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 subjects.

Pharmacokinetics in special populations:

The elderly:

In the elderly, the terminal plasma half-life of ketorolac is prolonged, compared to young, healthy volunteers, to an average of 7 hours, ranging from 4,3 – 8,6 hours. 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 subjects. 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

Disodium edetate

Hydrochloric acid (For pH-adjustment)

Potassium dihydrogen phosphate

Propylene glycol

Sodium chloride

Sodium hydroxide (For pH-adjustment)

Water for injection.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

BEDORAL ® 30 is a clear, colourless solution, free from visible particles and fibres.

2 ml clear USP type-1 glass ampoules each containing 1 ml solution

Ampoules are supplied in cartons of 10 ampoules.

6.6 Special precautions for disposal and other handling

For intramuscular or bolus intravenous injection.

For single use only. Discard any unused contents.

Any unused product or waste material should be disposed of.

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill

Ext.1

Roodepoort

1724

South Africa

8. REGISTRATION NUMBER

A40/2.7/0147

NS2	12/2.7/0015 (Namibia)

9. DATE OF FIRST AUTHORISATION

The date on the registration certificate of the medicine:

07 July 2006

10. DATE OF REVISION OF THE TEXT

18 October 2021