SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BETACIN® Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **BETACIN®** capsule contains 25 mg indometacin.

Contains sugar: lactose 86,83 mg per capsule

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules

BETACIN®

A size 3 yellow gelatine capsule imprinted with **BETACIN®** on the cap in red colour and black colour on the body, containing a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indomethacin is indicated for the symptomatic treatment of rheumatoid arthritis, ankylosing / spondylitis, osteoarthritis, other musculo-skeletal inflammatory disorders and acute attacks of gout.

4.2 Posology and method of administration

The recommended dosage is 25 mg to 200 mg daily divided in two to four equal doses, given with food, milk or an antacid. Therapy may be initiated with low doses and gradually increasing them where necessary according to the patients response and requirements.

Bioavailability may be reduced with antacids containing aluminium hydroxide, magnesium carbonate and magnesium hydroxide.

Use the lowest effective dose for the shortest possible duration of treatment.

Method of administration

BETACIN® is for oral administration.

4.3 Contraindications

Hypersensitivity to indomethacin or to any of the excipients of **BETACIN®** (see section 6.1)

BETACIN® should not be used in:

- Patients who have previously shown sensitivity to it indomethacin or to asprin
- Persons operating machinery, or patients with psychiatric disorders, epilepsy or parkinsonism
- Persons with renal disease or ulcerative lesions of the stomach or intestines.
- Patients with bleeding disorders, active peptic ulcers, gastritis, regional enteritis and ulcerative colitis
- Pregnant and nursing women
- Children.
- Heart failure**.**
- History of gastrointestinal bleeding or perforation (PUBs) related to previous NSAIDs
- Active or history of recurrent ulcer/haemorrhage/perforations.

4.4 Special warnings and precautions for use

Regular use of NSAIDs during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero and possibly in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased. Indomethacin is excreted in the breast milk of breast-feeding mothers. (See section 4.6).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **Betacin®** therapy.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of Betacin®, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving **BETACIN®,** treatment with **BETACIN®** should be stopped.

BETACIN® should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. **Betacin®** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **BETACIN®**. 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 **BETACIN®** and evaluate the patient immediately

Lactose

BETACIN® contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **BETACIN®**

4.5 Interaction with other medicines and other forms of interaction

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

- Antacids: the bioavailability of indometacin may be reduced by concomitant antacid therapy.
- Anticoagulants: NSAIDs may enhance the effects of anti- coagulants, such as warfarin.
- Antidepressants (SSRI): increased risk of bleeding
- Antidiabetics: the effect of sulfonylureas may be increased by NSAIDs.
- Antihypertensives: Reduced anti-hypertensive effect.

  Indometacin may acutely reduce the antihypertensive effect of beta-blockers due partly to indometacin's inhibition of prostaglandin synthesis. Patients receiving dual therapy should have the antihypertensive effect of their therapy reassessed.

  Therefore, caution should be exercised when considering the addition of indometacin to the regimen of a patient taking any of the following antihypertensive agents:

  alpha-adrenergic blocking agents, ACE inhibitors, beta-adrenergic blocking agents, Angiotensin-2-receptor antagonists, hydralazine or nifedipine. An increased risk of hyperkalaemia has also been reported when NSAIDs are taken with ACE inhibitors.
- Anti-platelet agents: increased risk of

gastrointestinal bleeding. Indometacin can inhibit platelet aggregation, an effect which disappears within 24 hours of discontinuation; the bleeding time may be prolonged and this effect may be exaggerated in patients with an underlying haemostatic defect.

- Antipsychotics: increased drowsiness with indometacin and haloperidol.
- Antivirals: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. Risk of indometacin toxicity with ritonavir, avoid concomitant use.
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma - cardiac glycoside levels.
- Ciclosporin: Increased risk of nephrotoxicity. Administration of NSAIDs concomitantly with ciclosporin has been associated with an increase in ciclosporin- induced toxicity, possibly due to decreased synthesis of renal prostacyclin.NSAIDs should be used with caution in patients taking ciclosporin, and renal function should be monitored carefully.
- Corticosteroids: Increased risk of gastro-intestinal ulceration or bleeding (see section 4.4). If the patient is receiving corticosteroids concomitantly, a reduction in dosage of these may be possible but should only be effected slowly under supervision.
- Cytotoxics: indometacin may decrease the tubular secretion of methotrexate thus potentiating toxicity; simultaneous useshould be undertaken with caution.
- Desmopressin: effect potentiated by indometacin.
- Diflunisal: avoid concomitant use. Increased plasma levels of indometacin by about a third with a concomitant decrease in renal clearance. Fatal gastro- intestinal haemorrhage has occurred.
- Diuretics: 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 angiotensin II receptor antagonists are combined with NSAIDs. Therefore,the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Indometacin may reduce the diuretic and anti-hypertensive effect of thiazides and furosemide in some patients.

Indometacin may cause blocking of the furosemide – induced increase in plasma renin activity. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

- Lithium: Decreased elimination of lithium. Indometacin is an inhibitor of prostaglandin synthesis and therefore the following drug interactions may occur; indomethacin may raise plasma lithium levels and reduce lithium clearance in subjects with steady state plasma lithium concentrations. At the onset of such combined therapy, plasma lithium concentration should be monitored more frequently
- Methotrexate*:* Decreased elimination of methotrexate.

  Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- Muscle Relaxants: increased risk of baclofen toxicity due to reduced rate of excretion.
- Pentoxifylline: possible increased risk of bleeding when taken with NSAIDs.
- Probenecid: co-administration of probenecid may Increase indometacin plasma levels. When increases in the dose of indometacin are made under these circumstances, they should be made cautiously and in small increments.
- Quinolone antibiotics*:* Animal data indicate the NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- Salicylates: use of indometacin with aspirin or other salicylates is not recommended

because there is no enhancement of therapeutic effect while the incidence of gastro-intestinal

- Tacrolimus: Possible increased risk of nephrotoxicity hen NSAIDs are given with tacrolimus.
- Tiludronic acid: the bioavailability of tiludronic acid is increased by indometacin.
- Triamterene: acute renal failure has been reported with concomitant indomethacin therapy.
- Laboratory tests: false-negative results in the dexamethasone suppression test (DST) in patients being treated with indometacin have been reported.

  Thus, results of this test should be used with caution in these patients.

4.6 Fertility, Pregnancy and Lactation

BETACIN® is contra-indicated in pregnant women.(See section 4.4)

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

4.7 Effects on ability to drive and use machines

Dizziness, light-headedness, drowsiness, fatigue, visual disturbances or vertigo are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

- *Blood and lymphatic system disorders:*

  Blood dyscrasias (such as thrombocytopenia, neutropenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia), bone marrow depression, petechiae,

ecchymoses, purpura,and disseminated intravascular coagulation may occur infrequently. As some patients manifest anaemia secondary to obvious or occult gastro-intestinal bleeding, appropriate blood determinations are recommended.

- *Immune system disorders:*

  Hypersensitivity reactions have been reported following treatment with NSAIDs. These mayconsist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, rhinitis or (c) assorted skin disorders, including rashes of various types, pruritus,urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

- *Metabolic and nutrition disorders**:***

  Hyperglycaemia, glycosuria, hyperkalaemia has been reported rarely.

- *Nervous system disorders:*

  Visual disturbances, optic neuritis, tinnitus, headache, dizziness and light headedness are common side effects**.** Starting therapy with a low dose and increasing gradually minimises the incidence of headache. These symptoms frequently disappear on continued therapy or reducing the dosage, but if headache persists despite dosage reduction, indomethacin should be withdrawn. Other CNS effects include reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus or mixed connective tissue disease)with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, vertigo, fatigue, malaise, dysarthria, syncope, coma, cerebral oedema, nervousness**,** confusion, anxiety and other psychiatric disturbances, depersonalisation, hallucinations**,** drowsiness, convulsions and aggravation of epilepsy and parkinsonism.

peripheral neuropathy, paraesthesia, involuntary movements and insomnia. These effects are often transient and abate or disappear on reduced or stopping treatment. However, the severity of these may, on occasion, require cessation of therapy

- *Eye disorders:*

  Visual disturbances, blurred vision, diplopia, optic neuritis and orbital and peri-orbital pain are seen infrequently. Corneal deposits and retinal or macular disturbances have been reported in some patients with rheumatoid arthritis on prolonged therapy with indometacin. Ophthalmic examinations are desirable in patients given prolonged treatment.

- *Ear and labyrinth disorders:*

  Tinnitus or hearing disturbances (rarely deafness) have been reported.

- *Cardiac disorders:*

  Oedema, hypertension, hypotension, tachycardia, chest pain, arrhythmia, palpitations, syncope and cardiac failure have been reported.

- Clinical trial and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke)

- *Vascular disorders:*

  Flushing has been reported rarely.

- *Respiratory, thoracic and mediastinal disorders*:

  Pulmonary eosinophilia. There may be bronchospasm in patients with a history of bronchial asthma or other allergic disease. Epistaxis has been reported rarely.

- *Gastrointestinal disorders:*

  The most commonly-observed adverse events are gastrointestinal in nature. Anorexia, epigastric discomfort, ulceration at any point in the gastro-intestinal tract (even with resultant stenosis and obstruction),bleeding (even without obvious ulceration or from a diverticulum) and perforation of pre-existing sigmoid lesions (such as diverticulum or carcinoma), increased abdominal pain or exacerbation of the condition in patients with ulcerative colitis or Crohns disease (or the development of this condition), intestinal strictures and regional ileitis have been rarely reported. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). If gastro-intestinal bleeding does occur treatment with indomethacin should be discontinued. Gastro-intestinal disorders which occurcan be reduced by giving indomethacin with food, milk or antacids. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

- *Hepatobiliary disorders:*

  Cholestasis, borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT) have been seen in less than 1% of patients receiving therapy with NSAIDs in controlled clinical trials. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop,or if systemic manifestations such as rash or eosinophilia occur, indomethacin should be stopped. Abnormal liver function,hepatitis and jaundice.

- *Skin and subcutaneous tissue disorders:*

Pruritus, urticaria, angioneurotic oedema, angiitis, photosensitivity, erythemanodosum, rash and exfoliative dermatitis, bullous reactions including Stevens Johnson syndrome, erythema multiforme,toxic epidermal necrolysis (very rare), hair loss, sweating and exacerbation of psoriasis.

Drug Reactions with Eosinophillia and Systemic Symptoms (DRESS) [see Section 4.4]

- *Musculo-skeletal and connective tissue disorders:*

  Muscle weakness and acceleration of cartilage degeneration.

- *Renal and urinary disorders:*

  Haematuria, nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure, renal insufficiency, proteinuria have all been reported. In patients with renal, cardiac or hepatic impairment, caution is required since the use of non-steroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored.

- *Reproductive system and breast disorders:*

  Vaginal bleeding, breast changes (enlargement, tenderness, gynaecomastia).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **BETACIN®** is important. It allows continued monitoring of the benefit/risk balance of **BETACIN®**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/

4.9 OVERDOSE

a) Symptoms:

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions, abdominal pain, anorexia, restlessness and agitation. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion o fa potentially life-threatening overdose. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category:A 3.1 antirheumatics (anti-inflammatory agents)

ATC code : M01A B01

Mechanism of action

Indomethacin is a non-steroidal anti-inflammatory drug with anti-inflammatory and analgesic properties which are mediated through It’s mode of action as an inhibitor of prostaglandin synthesis

The analgesic properties have been attributed to both central and peripheral effect, which are distinct from its anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption:

Indomethacin is rapidly and almost completely absorbed from the gastrointestinal tract following oral ingestion.

Peak plasma levels occur in 0.5-2 hours in fasting subjects, longer if taken with or after food.

Distribution:

More than 90% is bound to plasma proteins. It is distributed into synovial fluid, CNS and placenta. Low concentrations have been found in breast mik. The concentration in synovial fluid is equal to that in plasma within 5 hours

Indomethacin is largely converted to inactive metabolites.

Metabolism:

It is metabolised in the liver primarily by demethylation and deacetylation, it also undergoes glucuronidationand enterohepatic circulation. Enterohepatic cycling of metabolites, and probably indomethacin itself, occurs. Half-life in plasma is variable from 2 – 11 hours

Elimination:

Mainly excreted in the urine, approximately 60%, the pH of the urine can affect this amount. Lesser amounts in the faeces. Indometacin is also excreted in milk in small amounts.

5.3 Preclinical Safety Data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, microcrystalline cellulose (avicel ph 101), purified talc, sodium lauryl sulphate, sodium starch glycolate (explotab), starch maize (dried), tablettose (lactose).

Hard Gelatine Capsule

Quinoline yellow WS (C.I. 47005), sunset yellow FCF (C.I. 15985), titanium dioxide (CI 77891)

Red Marking Solution RDL001

Butyl alcohol, dehydrated alcohol, isopropyl alcohol, polysorbate 80, poncrea 4R lake, propylene glycol,

shellac, strong ammonia solution, titanium dioxide

Black Marking Solution BKI001

Black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, propylene glycol, shellac

6.2 Incompatibilities

None known

6.3 Shelf life

24 months for bottles containing 100, 500, 1000 capsules

15 months: Patient ready packs of different pack sizes

6.4 Special precautions for storage

Store in a dry place at or below 25°C.

Protect from light.

6.5 Nature and contents of container

Bottles containing 100, 500, 1000 capsules.

Patient ready packs of different pack sizes.

6.6 Special precautions for disposal

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(S)

X/3.1/0187 (S.A)

NS2 04/3.1/0993 (Namibia)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

01 October 1990

10. DATE OF REVISION OF THE TEXT

22 December 2021