Professional Information for INDOMETHACIN BIOTECH 25

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

INDOMETHACIN BIOTECH 25 Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each capsule contains indomethacin 25 mg.

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM:

Capsules, hard.

Opaque, yellow, hard gelatine capsule containing a white powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

INDOMETHACIN BIOTECH 25 is indicated in active stages of:

- rheumatoid arthritis;
- osteoarthritis;
- ankylosing spondylitis;
- degenerative joint disease of the hip;
- acute gouty arthritis.

INDOMETHACIN BIOTECH 25 is also indicated for:

- acute musculoskeletal disorders, such as, bursitis, tendonitis, synovitis, tenosynovitis, capsulitis

of the shoulder, sprains and strains;

- low back pain (commonly referred to as lumbago);
- fever (as a short-term adjunct to specific therapy);
- inflammation, pain, trismus and swelling following dental procedures;
- inflammation, pain and swelling following orthopaedic surgical procedures and nonsurgical procedures associated with reduction and immobilisation of fractures or dislocations;
- pain and associated symptoms of primary dysmenorrhoea

4.2 Posology and method of administration:

Posology:

Adults:

The recommended dose of INDOMETHACIN BIOTECH 25 is 50 mg to 200 mg daily in divided doses, individually adjusted to the patient's response and tolerability to the medicines. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals, starting with a low dose.

A loading dose of INDOMETHACIN BIOTECH 25 is not necessary. In chronic rheumatic disorders, initiating therapy with low doses, increasing gradually when necessary, and continuing for an adequate period (up to one month is recommended), will produce maximum benefit and minimise adverse reactions.

In patients with persistent night pain and/or morning stiffness, a dose of up to 100 mg at bedtime may be helpful in affording relief. A dosage of 200 mg per day should not be exceeded.

In the treatment of acute gouty arthritis, the recommended daily dosage of 150 mg to 200 mg in divided doses until symptoms and signs subside.

In primary dysmenorrhea, the recommended dosage is 75 mg daily as a single or divided dose,

starting at the onset of cramps and bleeding and continuing for as long as symptoms usually last.

To minimise or reduce the possibility of gastrointestinal disturbances, it is recommended that INDOMETHACIN BIOTECH 25 be taken with food, milk or an antacid. In chronic conditions start the therapy with a low dosage, increasing as required.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Paediatric population:

The safety and efficacy of indomethacin, as in INDOMETHACIN BIOTECH 25, in children have not been established.

4.3 Contraindications:

INDOMETHACIN BIOTECH 25 is contraindicated in:

- patients hypersensitive to indomethacin, or to aspirin or to any of the other ingredients of INDOMETHACIN BIOTECH 25 (see section 6.1);
- patients in whom acute asthmatic attacks, urticaria or rhinitis and nasal polyps are precipitated by acetylsalicylic acid (aspirin) or other nonsteroidal anti-inflammatory drugs (NSAIDs);
- INDOMETHACIN BIOTECH 25 and diflunisal should not be used concomitantly;
- persons operating machinery;
- patients with psychiatric disorders, epilepsy or Parkinsonism;
- patients with severe hepatic failure and renal failure;
- in patients with current and/ a history of perforation, peptic ulcers or active peptic ulcers or bleeding (PUBS) related to previous NSAIDs, including INDOMETHACIN BIOTECH 25, gastritis, regional enteritis and ulcerative colitis, or with a recurrent history of gastrointestinal ulceration;
- patients with a history of, or current gastrointestinal lesions, including ulcer, haemorrhage or perforations;

- patients with a history of angioedema following exposure to NSAIDs and/ or aspirin;
- the treatment of peri-operative pain relief in the setting of coronary artery surgery;
- patients with heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke), and peripheral arterial disease;
- pregnancy and lactation (see section 4.6);

The safety of INDOMETHACIN BIOTECH 25 in children has not been established.

4.4 Special warnings and precautions for use:

INDOMETHACIN BIOTECH 25 may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs, such as INDOMETHACIN BIOTECH 25 at higher than recommended doses (see sections 4.8 and 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. NSAID-induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

The use of INDOMETHACIN BIOTECH 25 with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided (see section 4.5).

INDOMETHACIN BIOTECH 25 should be used cautiously in patients with impaired renal function and bleeding disorders, as it may tend to aggravate these. INDOMETHACIN BIOTECH 25 is contraindicated in patients with severe renal failure, psychiatric disorders, epilepsy or Parkinsonism (see section 4.3).

Patients should be carefully observed to detect any unusual manifestations of medicine sensitivity.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension, as fluid retention and oedema have been reported in association with NSAID therapy (see below).

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

There are insufficient data to exclude such a risk for INDOMETHACIN BIOTECH 25.

Patients with uncontrolled hypertension should only be treated with INDOMETHACIN BIOTECH 25 after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

INDOMETHACIN BIOTECH 25 is contraindicated in patients with heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke), and peripheral arterial disease (see section 4.3).

Hypertension:

NSAIDs, including INDOMETHACIN BIOTECH 25, can lead to onset or exacerbation of hypertension, either of which may contribute to the increased incidence of cardiovascular events.

Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including INDOMETHACIN BIOTECH 25, 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, fluid retention and oedema:

Congestive heart failure, fluid retention and peripheral oedema have been observed in some patients taking INDOMETHACIN BIOTECH 25. Thus, INDOMETHACIN BIOTECH 25 should be used with caution in patients with cardiac dysfunction, hypertension or other conditions predisposing to fluid

retention.

In view of the inherent potential of INDOMETHACIN BIOTECH 25 to cause fluid retention, heart failure may be precipitated in some compromised patients.

Infection:

INDOMETHACIN BIOTECH 25 may mask the signs and symptoms of infection, so antibiotic therapy should be initiated promptly if an infection occurs during therapy with INDOMETHACIN BIOTECH 25. It should be used cautiously in patients with existing but controlled infection. Caution is advised with concomitant use of live vaccines.

Ocular effects:

During prolonged therapy, periodic ophthalmic examinations are recommended, as corneal deposits and retinal disturbances have been reported. In patients with rheumatoid arthritis, eye changes may occur, which may be related to the underlying disease or to the therapy.

Therefore, in chronic rheumatoid disease, ophthalmological examinations are periodic intervals are recommended. Therapy should be discontinued if eye changes are observed.

Cardiovascular, renal and hepatic impairment:

In patients with renal, cardiac, hepatic impairment, hypertension or conditions predisposing to fluid retention, caution is required since the use of NSAIDs may result in deterioration of renal function (see section 4.8). The dose should be kept as low as possible and renal function should be monitored. NSAIDs may also cause fluid retention which may further aggravate these conditions. INDOMETHACIN BIOTECH 25 is contraindicated in patients with severe renal and hepatic failure (see section 4.3).

There have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving long-term administration of INDOMETHACIN BIOTECH 25. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal

injury.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a NSAID may precipitate overt renal decompensation. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction, are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, the elderly, diabetes mellitus, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic medicine. INDOMETHACIN BIOTECH 25 should be given with caution and renal function should be monitored in these patients (see section 4.3). Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Since INDOMETHACIN BIOTECH 25 is eliminated primarily by the kidneys (see section 5: Elimination), patients with significantly impaired renal function should not be treated with INDOMETHACIN BIOTECH 25.

Elderly patients:

Elderly patients may be especially susceptible to the toxic effects of INDOMETHACIN BIOTECH 25. Elderly patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal perforation, ulceration, and bleeding (PUBs) which may be fatal.

Respiratory disorders:

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Drug reaction with eosinophilia and systemic symptoms (DRESS):

DRESS has been reported in patients taking NSAIDs, such as INDOMETHACIN BIOTECH 25, 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. Eosinophilia 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 INDOMETHACIN BIOTECH 25 and evaluate the patient immediately.

Gastrointestinal (GI) effects:

Gastrointestinal disturbances may be minimised by giving INDOMETHACIN BIOTECH 25 orally with food, milk or an antacid, although the bioavailability of the medicine may be reduced with antacids containing aluminium hydroxide, magnesium carbonate and magnesium hydroxide. Gastrointestinal disturbances usually disappear on reducing the dosage; if not, the risks of continuing therapy should be weighed against the possible benefits.

Caution is advised in patients with pre-existing sigmoid lesions (such as diverticulum or carcinoma), or the development of these conditions, or a history of gastrointestinal disease (e.g., ulcerative colitis, Crohn's disease, hiatus hernia, gastroesophageal reflux disease, angiodysplasia, as INDOMETHACIN BIOTECH 25 can aggravate these conditions.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly during the initial stages of treatment. GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or previous history of serious GI events. When GI bleeding or ulceration occurs in patients receiving INDOMETHACIN BIOTECH 25, the treatment should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3),

and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective medicines (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk (see below and section 4.5).

Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, or antiplatelet medicines such as aspirin (see section 4.5).

Systemic lupus erythematosus (SLE) and mixed connective tissue disease:

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

Platelet aggregation:

INDOMETHACIN BIOTECH 25 should be used with caution in patients with coagulation defects as INDOMETHACIN BIOTECH 25 can inhibit platelet aggregation. This effect may be exaggerated in patients with underlying haemostatic defects. Inhibition of platelet aggregation usually disappears within 24 hours of discontinuing INDOMETHACIN BIOTECH 25.

Caution is required in post-operative patients as bleeding time is prolonged (but within normal range) in normal adults.

Because of its lack of platelet effects, INDOMETHACIN BIOTECH 25 is not a substitute for aspirin for cardiovascular prophylaxis.

Central nervous system effects:

Headache, sometimes accompanied by dizziness or light-headedness may occur, usually early in

treatment with INDOMETHACIN BIOTECH 25.

Starting therapy with a low dosage and increasing it gradually may minimise the incidence of headache. These symptoms may disappear on continuing therapy or with reducing the dosage. If headache persists despite dosage reduction, INDOMETHACIN BIOTECH 25 should be withdrawn.

Use in pregnancy:

INDOMETHACIN BIOTECH 25 is contraindicated during pregnancy (see section 4.3).

The use of NSAIDs, such as INDOMETHACIN BIOTECH 25, 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. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases (see section 4.6).

Hepatic effects:

INDOMETHACIN BIOTECH 25 may cause a rise in liver enzymes.

Significant (3-times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) in controlled clinical trials have been reported in less than 1 % of patients receiving therapy with NSAIDs such as INDOMETHACIN BIOTECH 25.

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 development of more severe hepatic reactions while on therapy with INDOMETHACIN BIOTECH 25.

If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), therapy should be discontinued.

Medication overuse headache (MOH):

After long-term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics, MOH, should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with MOH should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Avoid concomitant use of two or more NSAIDs.

Skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN), 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 reaction occurring in the majority of cases within the first month of treatment. INDOMETHACIN BIOTECH 25 should be discontinued at the first appearance of skin rash, mucosal lesions, and any other sign of hypersensitivity.

Plasma potassium:

Increases in plasma potassium concentration, including hyperkalaemia have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninaemic-hypoaldosteronism state.

General:

Patients should be periodically observed to allow early detection of any unwanted effects on peripheral blood (anaemia), liver function (see section 4.8), or gastrointestinal tract especially during prolonged therapy.

Paediatric population:

The safety of INDOMETHACIN BIOTECH 25 in children has not been established (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction:

INDOMETHACIN BIOTECH 25 inhibits platelet aggregation but is not a substitute for aspirin for cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with INDOMETHACIN BIOTECH 25.

Other analgesics, including cyclooxygenase-2 selective inhibitors:

The concomitant use of INDOMETHACIN BIOTECH 25 with other NSAIDs is not recommended, due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy

Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Antacids:

The bioavailability of INDOMETHACIN BIOTECH 25 may be reduced by concomitant antacid therapy.

Anticoagulants:

INDOMETHACIN BIOTECH 25 did not influence the hypoprothrombinaemia produced by anticoagulants in patients and in normal subjects. Patients should, however, be closely observed for alterations of prothrombin time, when INDOMETHACIN BIOTECH 25 is given concomitantly with anticoagulants. Caution should be exercised when INDOMETHACIN BIOTECH 25 and anticoagulants are administered concomitantly. Concurrent administration of oral anticoagulant medicines leads to increased risk of gastrointestinal bleeding.

NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

Antidepressants (SSRI):

Increased risk of bleeding (see section 4.4).

Antidiabetic medicines:

The hypoglycaemic effect of sulfonylureas may be increased by NSAIDs.

Antihypertensive medicines:

Reduced antihypertensive effect. INDOMETHACIN BIOTECH 25 may acutely reduce the antihypertensive effect of beta-blockers due partly to the inhibition of INDOMETHACIN BIOTECH 25 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 INDOMETHACIN BIOTECH 25 to the regimen of a patient taking any of the following antihypertensive medicines:

- alpha-adrenergic blocking medicines;
- ACE inhibitors;
- beta-adrenergic blocking medicines;
- angiotensin-2-receptor antagonists;
- hydralazine or nifedipine.

An increased risk of hyperkalaemia has also been reported when NSAIDs are taken with ACE inhibitors.

Antiplatelet medicines:

Increased risk of gastrointestinal bleeding. Indomethacin, as in INDOMETHACIN BIOTECH 25, 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 (see section 4.4).

Antipsychotics:

Increased drowsiness has been reported with concomitant use of INDOMETHACIN BIOTECH 25 and haloperidol.

Antivirals:

There is an increased risk of haematological toxicity when NSAIDs, such as INDOMETHACIN BIOTECH 25, are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV-positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. There is a risk of indomethacin toxicity with concomitant use of INDOMETHACIN BIOTECH 25 and ritonavir, and should thus be avoided.

Cardiac glycosides/digoxin:

INDOMETHACIN BIOTECH 25 given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when INDOMETHACIN BIOTECH 25 and digoxin are used concomitantly, plasma digoxin levels should be closely monitored.

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma-cardiac glycoside levels.

Calcineurin inhibitors:

Increased risk of nephrotoxicity. Administration of NSAIDs, such as INDOMETHACIN BIOTECH 25, concomitantly with calcineurin inhibitors, including ciclosporin and tacrolimus, has been associated with an increase in toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking calcineurin inhibitors, and renal function should be monitored carefully.

Phenylpropanolamine:

Hypertensive crises have been reported due to oral phenylpropanolamine, and to

phenylpropanolamine given concomitantly with INDOMETHACIN BIOTECH 25. This additive effect is probably due at least in part to inhibition of prostaglandin synthesis by indomethacin, as in INDOMETHACIN BIOTECH 25, and may lead to water intoxication. Caution should be exercised when INDOMETHACIN BIOTECH 25 and phenylpropanolamine are administered concomitantly.

Corticosteroids:

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs) (see section 4.4). If the patient is receiving corticosteroids concomitantly, a reduction in dosage of these may be possible but should only be affected slowly under supervision.

Cytotoxic medicines:

INDOMETHACIN BIOTECH 25 may decrease the tubular secretion of methotrexate thus potentiating toxicity; simultaneous use should be undertaken with caution.

Desmopressin:

Effect potentiated by indomethacin, as in INDOMETHACIN BIOTECH 25, my lead to water intoxication.

Diflunisal:

Avoid concomitant use (see section 4.3). Coadministration of diflunisal and INDOMETHACIN BIOTECH 25 increases the plasma level of indomethacin by about a third, with a concomitant decrease in renal clearance. Fatal gastrointestinal haemorrhage has occurred.

Diuretics:

NSAIDs, such as INDOMETHACIN BIOTECH 25, may reduce the effect of diuretics and antihypertensive medicines. In patients with compromised renal function (e.g., dehydrated patients (volume depleted patients, including those on diuretic therapy) or the elderly patients) who are being treated with NSAIDs including selective cyclooxygenase-2 inhibitors, the coadministration of

angiotensin II receptor antagonists or ACE inhibitors may result in further deterioration of renal function, including possible acute renal injury (renal failure). These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

INDOMETHACIN BIOTECH 25 can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium sparing, thiazide diuretics and furosemide. Therefore, when INDOMETHACIN BIOTECH 25 and diuretics are used concomitantly, the patient should be closely observed to determine whether the desired effect of the diuretic is being obtained.

INDOMETHACIN BIOTECH 25 may cause blocking of the furosemide-induced increase in plasma renin activity (PRA).
INDOMETHACIN BIOTECH 25 reduces basal PRA as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of INDOMETHACIN BIOTECH 25 resulted in reversible acute renal injury (acute renal failure). INDOMETHACIN BIOTECH 25 and triamterene should not be administered concomitantly.

Both INDOMETHACIN BIOTECH 25 and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of INDOMETHACIN BIOTECH 25 and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these medicines are administered concurrently.

Most of the above effects relating to diuretics have been attributed at least in part, to mechanisms involving inhibition of prostaglandin synthesis in INDOMETHACIN BIOTECH 25.

Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Lithium:

Decreased elimination of lithium. INDOMETHACIN BIOTECH 25 is an inhibitor of prostaglandin synthesis and therefore the following interactions may occur: INDOMETHACIN BIOTECH 25 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:

*C*aution should be exercised with concomitant use of INDOMETHACIN BIOTECH 25, with methotrexate.

Indomethacin, as in INDOMETHACIN BIOTECH 25, has been reported to decrease the tubular secretion of methotrexate and thereby to potentiate methotrexate toxicity.

Serious interactions have been reported with the use of high doses of methotrexate with INDOMETHACIN BIOTECH 25.

Mifepristone:

NSAIDs, such as INDOMETHACIN BIOTECH 25, and aspirin should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Muscle relaxants:

Concomitant use of NSAIDs, such as INDOMETHACIN BIOTECH 25, and baclofen may induce baclofen toxicity due to a reduced rate of excretion.

Pentoxifylline:

Possible increased risk of bleeding when taken with NSAIDs.

Probenecid:

Coadministration of probenecid may increase indomethacin and its inactive metabolites plasma levels. Therefore, a lower total daily dosage in INDOMETHACIN BIOTECH 25 may produce a satisfactory therapeutic effect. When increases in the dose of INDOMETHACIN BIOTECH 25 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 INDOMETHACIN BIOTECH 25 and quinolones may have an increased risk of developing convulsions.

Salicylates:

The use of INDOMETHACIN BIOTECH 25 with aspirin or other salicylates is not recommended because there is no enhancement of therapeutic effect while the incidence of gastrointestinal adverse effects is increased. Moreover, coadministration of aspirin may decrease the blood concentration of INDOMETHACIN BIOTECH 25.

Tiludronic acid:

The bioavailability of tiludronic acid is increased by indomethacin, as in INDOMETHACIN BIOTECH 25.

Laboratory tests:

False-negative results in the dexamethasone suppression test (DST) in patients being treated with INDOMETHACIN BIOTECH 25 have been reported. Thus, the results of this test should be used with caution in these patients.

4.6 Fertility, pregnancy and lactation:

The use of INDOMETHACIN BIOTECH 25 is contraindicated in pregnancy and lactation (see section

4.3).

Pregnancy:

INDOMETHACIN BIOTECH 25 is contraindicated in pregnant women (see section 4.3 and 4,4). Regular use of nonsteroidal anti-inflammatory drugs, such as INDOMETHACIN BIOTECH 25, 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 new-born. The onset of labour may be delayed and its duration increased.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation 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 %. The risk is believed to increase with dose and duration of therapy. 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.

During the third trimester of pregnancy, all 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 oligohydroamniosis;

May expose the mother and the neonate, at the end of pregnancy to:

- possible prolongation of bleeding time, an antiaggregating effect, which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Lactation:

INDOMETHACIN BIOTECH 25 is excreted in the breast milk of breastfeeding mothers.

INDOMETHACIN BIOTECH 25 should not be used by mothers who are breastfeeding their infants (see section 4.3).

Impaired female fertility:

The use of INDOMETHACIN BIOTECH 25 may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of INDOMETHACIN BIOTECH 25 should be considered.

4.7 Effects on ability to drive and use machines:

INDOMETHACIN BIOTECH 25 may interfere with driving and the operation of machines, as it may cause dizziness, drowsiness, visual disturbances and headaches.
INDOMETHACIN BIOTECH 25 is contraindicated in persons operating machinery (see section 4.3).

4.8 Undesirable effects:

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations		Fulminant necrotising fasciitis; particularly in association with Group A β-haemolytic streptococcus	
Neoplasm benign, malignant and unspecified (including			Leukaemia

cysts and polyps)		
Blood and lymphatic system disorders	Blood dyscrasias may occur, including leucopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia, agranulocytosis, bone marrow depression, disseminated intravascular coagulation, and thrombocytopenia. As some patients manifest anaemia secondary to obvious or occult gastrointestinal bleeding, appropriate blood determinations are recommended.	
Immune system disorders	Acute anaphylaxis	Hypersensitivity reactions: (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, angioedema and exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)
Metabolism and nutrition disorders		Hyperglycaemia, glycosuria, hyperkalaemia	Weight gain
Psychiatric disorders	Mental confusion, anxiety, psychic disturbances such as depersonalisation, psychotic episodes, aggravation of psychiatric disturbances		Depression, drowsiness, confusion, insomnia, hallucinations
Nervous system disorders	Headache, dizziness, light-headedness.	Vertigo, fatigue (including malaise and listlessness) syncope, drowsiness, convulsions, coma,	Aseptic meningitis (especially in patients with existing autoimmune

	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 BIOTECH 25 should be withdrawn.	peripheral neuropathy, involuntary muscle movement, dysarthria, epilepsy, parkinsonism, mental confusion, anxiety, muscle weakness	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, dysarthria, coma, cerebral oedema, nervousness, hallucinations, drowsiness, convulsions and aggravation of epilepsy and parkinsonism, paraesthesia, involuntary movements. 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	Optic neuritis	Visual disturbances, blurred vision, diplopia, and orbital and peri-orbital pain	Corneal deposits, retinal disturbances, including those of the macula
Ear and labyrinth disorders	Tinnitus		Hearing disturbances, deafness
Cardiac disorders		Myocardial infarction, cardiovascular thrombotic events. 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) (see section 4.4).	Peripheral oedema, tachycardia, dysrhythmia, palpitations, congestive heart failure, chest pain, palpitations, cardiac failure
Vascular disorders		Flushing	Elevation of blood pressure (hypertension),

			hypotension, thrombophlebitis
Respiratory, thoracic and mediastinal disorders		Epistaxis, acute respiratory distress, sudden dyspnoea, asthma, pulmonary oedema	Pulmonary eosinophilia, bronchospasm
Gastrointestinal disorders	The most commonly observed adverse events are gastrointestinal in nature. Gastrointestinal disturbances, epigastric distress, abdominal laceration (single or multiple) of oesophagus, stomach, duodenum or small or large intestine, including perforation and haemorrhage	Tenesmus, proctitis, rectal bleeding, burning, pain, discomfort, itching or irritation; pancreatitis, regional ileitis, anorexia, epigastric discomfort, ulceration at any point in the gastrointestinal 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 intestinal strictures and regional	Peptic ulcers, perforation, or gastrointestinal bleeding, sometimes fatal. nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease

		gastritis	
Hepatobiliary disorders	Jaundice and hepatitis		Cholestasis, borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT), abnormal liver function, hepatitis and jaundice. 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 BIOTECH 25 should be stopped
Skin and subcutaneous tissue disorders	Erythema, angiitis, photosensitivity	Petechiae, ecchymosis, purpura, flushing exfoliative dermatitis, bullous reactions, Stevens Johnson syndrome,	Pruritus, urticaria, angioedema, photosensitivity, rash, hair loss, sweating, exacerbation of

		erythema multiforme, toxic epidermal necrolysis	psoriasis
Musculoskeletal and connective tissue disorders			Muscle weakness, acceleration of cartilage degeneration
Renal and urinary disorders	Elevation of blood urea	Glycosuria, urinary frequency	Haematuria, nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, renal failure, renal insufficiency, proteinuria
Reproductive system and breast disorders			Breast changes (including enlargement, tenderness or gynaecomastia), vaginal bleeding
General disorders and administrative site conditions			Fatigue, chest pain
Investigations	BUN elevation	A rapid fall in blood pressure resembling a shock-like state, borderline elevations of one or more liver tests may occur, and	

	significant elevations of ALT (SGPT) or AST (SGOT), false-negative results in the dexamethasone suppression test (DST)

Post-marketing experience:

System organ class	Frequency unknown
Metabolism and nutrition disorders	Hypokalaemia*
Renal and urinary disorders	Renal tubular acidosis*

*See sections 4.8 and 4.9.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of INDOMETHACIN BIOTECH 25 is important. It allows continued monitoring of the benefit/risk balance of INDOMETHACIN BIOTECH 25. 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/Publications/Index/8

4.9 Overdose

Symptoms:

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

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness

(see sections 4.4 and section 4.8).

Treatment:

Treatment is supportive and symptomatic.

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 of a 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:

Category and class: A 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids: Acetic acid derivatives and related substances

ATC code: M01AB01

Indomethacin is a nonsteroidal anti-inflammatory drug, with anti-inflammatory and analgesic properties, which is mediated through its mode of action as an inhibitor of prostaglandin synthesis.

Indomethacin affords relief of symptoms; it does not alter the course of the underlying disease.

5.2 Pharmacokinetic properties:

Absorption:

Following a single oral dose, indomethacin is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin is virtually 100 % bioavailable, with 90 % of the dose absorbed within 4 hours.

Distribution:

Indomethacin exists in the plasma as the parent medicine and its dimethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 % of an oral dosage is recovered in urine as medicine and metabolites (26 % as indomethacin and its glucuronide), and 33 % is recovered in faeces (1,5 % as indomethacin).

About 99 % of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin crosses the blood-brain barrier and the placenta.

Biotransformation:

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

Elimination:

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4,5 hours. With a typical therapeutic regimen of 25 or 50 mg three times daily, the steady-state plasma concentrations of indomethacin are an average 1,4 times those following the first dose.

Special populations:

Elderly patients:

An increase in age increases the possibility of side effects. Indomethacin should be used with greater care in the elderly.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Colloidal silicon dioxide (aerosil)

Magnesium stearate

Pre-gelatinised starch

Sodium lauryl sulphate

Talc.

Capsule shell: Erythrosine, quinolene yellow and titanium dioxide.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months (2 years)

6.4 Special precautions for storage:

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

6.5 Nature and contents of container:

INDOMETHACIN BIOTECH 25 capsules are supplied in white, polypropylene securitainers of 100 and 500 capsules, amber glass bottles of 100 and 500 capsules, while, high density polyethylene containers of 500 and 1 000 capsules, and PVC/ aluminium blisters of 15 and 84 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road

Randjespark, Halfway House

Midrand 1685

8. REGISTRATION NUMBER:

U/3.1/177

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

18 August 1987

10. DATE OF REVISION OF THE TEXT:

06 July 2023