SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indometacin 25 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25mg Indometacin.

Excipients with known effect: Also contains 145.10 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule

A hard white capsule printed with 'BL 25' containing a white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indometacin is a non-steroidal anti-inflammatory agent indicated for the following conditions:

- Active stages of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, degenerative joint disease of the hip, low back pain and acute gouty arthritis.
- It is also indicated for pain, inflammation and oedema following orthopaedic procedures.
- Treatment of pain and associated symptoms of primary dysmenorrhoea.

4.2 Posology and method of administration

Posology

The dosage of Indometacin should be carefully adjusted according to the needs of the individual patient.

To reduce the possibility of gastro-intestinal disturbances, Indometacin Capsules should always be taken with food, milk or an antacid.

Chronic condition: In chronic conditions, starting therapy with a low dosage, increasing this gradually as necessary, and continuing a trial of therapy for an adequate period (in some cases, up to one month) will give the best results with a minimum of unwanted reactions. The recommended oral dosage range is 50 mg to 200 mg daily in divided doses. Paediatric dosage not established.

Dosage in dysmenorrhoea: Up to 75 mg a day, starting with onset of cramps or bleeding, and continuing for as long as the symptoms usually last.

Dosage in acute gouty arthritis: 150 mg to 200 mg daily in divided doses until all symptoms and signs subside.

Use in the elderly: Indometacin should be used with particular care in older patients who are more prone to adverse reactions.

Paediatric population: The safety and efficacy of indometacin in children has not yet been established.

Method of Administration
For oral administration
To be taken preferably with or after food

4.3 Contraindications

- NSAIDs are contra-indicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non- steroidal anti-inflammatory drugs.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe heart failure, hepatic failure and renal failure (See section 4.4).
- Not to be used in patients who have nasal polyps.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- *Pregnancy and lactation*: Indometacin should not be used during third trimester of pregnancy or lactation (see section 4.6 'Pregnancy and lactation').
- Safety in children has not been established.

4.4 Special warnings and precautions for use

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

The use of indometacin capsules with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided (See section 4.5).

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.

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 Indometacin.

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with indometacin 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 and smoking).

Indometacin should be used cautiously in patients with impaired renal function, bleeding disorders, psychiatric disorders, epilepsy or Parkinsonism, as it may tend to aggravate these.

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

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 at periodic intervals are recommended. Therapy should be discontinued if eye changes are observed.

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

Cardiovascular, Renal and Hepatic Impairment:
In patients with renal, hepatic, cardiac impairment, hypertension, heart failure 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.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of 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 drug. Indometacin should be given with caution and renal function should be monitored in patients (see also section 4.3).

Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Elderly:
The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal (See section 4.2).

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.

Gastrointestinal bleeding, ulceration and perforation:
Gastro-intestinal disturbances may be minimised by giving indometacin orally with food, milk or an antacid. They 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) as indometacin can aggravate these conditions.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in 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 a previous history of serious GI events. When GI bleeding or ulceration occurs in patients receiving indometacin, 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 agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients

requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (See section 4.5).

NSAIDs should only be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (See section 4.8).

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematous (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (See section 4.8).

Impaired female fertility:
Indometacin may have a reversible inhibitory effect on women's ovulation. The use of indometacin 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 indometacin should be considered.

Indometacin should be used with caution in patients with coagulation defects as indometacin 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 indometacin.

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

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.

Headache, sometimes accompanied by dizziness and light-headedness, may occur, usually early in treatment. Starting therapy with a low dosage and increasing it gradually will usually minimise the incidence of headache. These symptoms frequently disappear on continuing therapy or reducing the dosage, but if headache and dizziness persist despite dosage reduction, indometacin should be withdrawn.

Medication Overuse Headache (MOH):
After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH-medication overuse headache) should be suspected in patients who have frequent or daily headache despite (or because of) regular use of analgesics. Patients with medication overuse headache 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.

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

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.

Important information regarding the Ingredients of Indometacin Capsules

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

Sodium: Indometacin capsules contain less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products 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 (see section 4.4).

Antacids: the bioavailability of indometacin may be reduced by concomitant antacid therapy.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

Anti-diabetics: The effect of sulphonylureas may be increased by NSAIDs.

Antidepressants (SSRI): increased risk of bleeding (see section 4.4)

Antihypertensives: Reduced anti-hypertensive effect. Indometacin may acutely reduce the antihypertensive effect of beta-blockers due partly to indometacin's inhibition of prostaglidin 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.

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 administrated 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 antihypertensive affect of thiazides and furosemide in some patients. Indometacin may cause blocking of the furosemide induced increase in plasma rennin activity. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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 (see section 4.4).

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 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 gastrointestinal 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 use should be undertaken with caution.

Desmopressin: effect potentiated by indometacin.

Diflunisal: avoid concomitant use. Increased plasma level of indometacin by about a third with a concomitant decrease in renal clearance. Fatal gastro-intestinal haemorrhage has occurred.

Lithium: Decreased elimination of lithium.
Indometacin is an inhibitor of prostaglandin synthesis and therefore the following drug reaction may occur; indometacin may raise plasma lithium levels and reduce lithium clearance in subjects with steady state plasma lithium concentration. At the onset of such combined therapy, plasma lithium concentrations 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 plasma levels of indometacin. 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 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.

Salicylates: The 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 side-effects is increased. Moreover, coadministration of aspirin may decrease the blood concentrations of indometacin.

Tacrolimus: Possible increased risk of nephrotoxicity when 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 indometacin 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.

Vancomycin: Studies in premature neonates being treated for patent ductus arteriosus have shown that concomitant administration of indometacin and vancomycin may have additive nephrotoxic effects. As such, caution is advised during concurrent or subsequent use of indometacin and vancomycin, as indometacin may increase the risk of vancomycin related toxicities. Where possible, monitor vancomycin levels and adjust the vancomycin dose and/or dosing interval accordingly.

4.6 Fertility, pregnancy and lactation

Pregnancy:
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.

From the 20th week of pregnancy onward, Indometacin use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, indometacin should not be given unless clearly necessary. If indometacin is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to indometacin for several days from gestational week 20 onward. Indometacin should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, indometacin is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Studies in animals have shown reproductive toxicity (see section 5.3)

Breast-feeding:
In the limited studies so far available, NSAIDs can appears in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding. Administration of indometacin is not recommended in breast-feeding mothers. Indometacin is excreted in breast milk.

Fertility:
For impaired female fertility, See section 4.4. See also section 5.3.

4.7 Effects on ability to drive and use machines

Undesirable effects such as 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

- *Nervous system disorders*- Visual disturbances, optic neuritis, tinnitus, headaches, 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 and dizziness persists despite dosage reduction, indometacin 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 the therapy.

- *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 Crohn's 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 indometacin should be discontinued. Gastrointestinal disorders which occur can be reduced by giving indometacin 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, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed. Pancreatitis has been reported very rarely.

- *Cardiac disorder* – There have been reports of oedema, hypertension, tachycardia, chest pain, arrhythmia, palpitations, hypotension, syncope and cardiac failure.

- *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.

- *Skin and subcutaneous tissue disorders:* Pruritus, urticaria, angioneurotic oedema, angiitis, erythema nodosum, rash, photosensitivity, exfoliative dermatitis, bullous reactions including Stevens Johnson syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity, erythema multiforme, hair loss, sweating and exacerbation of psoriasis

- *Musculo-skeletal, connective tissue and bone disorders:* Muscle weakness and acceleration of cartilage degeneration.

- *Hypersensitivity:* Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist 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, erythema multiforme).

- *Blood and lymphatic 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 patient manifest anaemia secondary to obvious or occult gastro-intestinal bleeding, appropriate blood determinations are recommended.

- *Metabolic and nutrition disorders:* Hyperglycaemia, glycosuria, hyperkalaemia have been reported rarely.

- *Eye disorder*- 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 rheumatoidnarthritis 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.

- *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.

- *Hepato-biliary 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, indometacin should be stopped. Abnormal liver function, hepatitis and jaundice.

- *Reproductive system and breast disorders:* Vaginal bleeding, breast changes (enlargement, tenderness, gynaecomastia)

- 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) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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.

Therapeutic measures
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 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

Pharmacotherapeutic group: Anti-inflammatory and Antirheumatic Products, Non-Steroids

ATC code: M01AB01

Indometacin is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties.

The anti-inflammatory effect is due to inhibition of prostaglandin synthesis, which is dose related and reversible.

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

5.2 Pharmacokinetic properties

Absorption: Indometacin is rapidly and almost completely absorbed from the gastrointestinal tract following oral ingestion; peak plasma concentrations are reached in about ½ to 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 milk. The concentration in synovial fluid is equal to that in plasma within 5 hours. Indometacin is largely converted to inactive metabolites.

Metabolism: It is metabolised in the liver primarily by demethylation and deacetylation, it also undergoes glucuronidation and enterohepatic circulation. Enterohepatic cycling of metabolites, and probably indometacin 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

Administration of indometacin to experimental animals at doses of 0.1-1.94 times the MRHD resulted in: i) maternal toxicity and death, ii) increased pre- and post-implantation loss. iii) increased embryotoxicity, foetal resorptions and foetal death, and iv) increased spontaneous abortion.

In pregnant mice and rats, indometacin treatment (during organogenesis) induced developmental defects including retarded foetal ossification and skeletal malformations at doses of 0.02-0.95 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose
Sodium starch glycolate
Magnesium stearate

Capsule shell
Gelatin Titanium dioxide E171 (Cap and Body)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.
Protect from light.

6.5 Nature and contents of container

An amber glass bottle with a tin-plate screw cap fitted with a waxed aluminium faced pulpboard liner.

Pack size: 250, 500 capsules

Or

Blister packs comprising of 250 micron PVC and 20 micron clear Aluminium foil

Pack sizes: 28 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd.
Unit 3, Canalside,
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8. MARKETING AUTHORIZATION NUMBER

PL 17907/0173

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation - 16th February 2005
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10 DATE OF REVISION OF THE TEXT

17/06/2026