SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pardelprin MR Capsules 75mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75mg of Indometacin

3 PHARMACEUTICAL FORM

Dark blue (head) and clear (body) hard gelatin Size 2 capsules printed “C” and “IR” in grey

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indometacin has non-steroidal analgesic and anti-inflammatory properties.

It is indicated for the following conditions:

- active stages of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, degenerative joint disease of the hip, acute musculoskeletal disorders and low back pain
- periarticular disorders such as bursitis, tendinitis, synovitis, tenosynovitis and capsulitis
- inflammation, pain and oedema following orthopaedic procedures
- treatment of pain and associated symptoms of primary dysmenorrhoea

4.2 Posology and method of administration

Method of Administration

For oral administration

Pardelprin should always be given with food or milk to reduce the chance of gastro-intestinal disturbance.

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

Adults: One capsule once or twice daily, depending on patient needs and response.

Dysmenorrhoea: One capsule a day, starting with onset of cramps or bleeding, and continuing for as long as symptoms usually last.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy

Children: Safety for use in children has not been established (see Section 4.3).

4.3 Contraindications

- Hypersensitivity to indometacin or to any of the excipients.
- NSAIDs are contraindicated in patients with angioneurotic oedema.
- NSAIDs are contraindicated 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.
- 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.
- Severe heart failure, hepatic failure and renal failure (see section 4.4).
- Not to be used in patients with nasal polyps.
- During the last trimester of pregnancy (see section 4.6).
- 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 with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided (see section 4.5)
- 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 persists despite dosage reduction, indometacin should be withdrawn. Patients should be warned that they may experience dizziness and, if they do, should not drive a car or undertake potentially dangerous activities needing alertness.

- *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)
- Particular care should be taken with older patients who are more susceptible to side-effects from indometacin (see section 4.2).

- *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 ischaemic 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, smoking).

- *Cardiovascular, Renal and Hepatic Impairment:*
  In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, 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, liver dysfunction, cardiac impairment, 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 these patients (see also section 4.3) Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.
- In patients with renal, cardiac, hepatic 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.
- As with other non-steroidal anti-inflammatory drugs, there have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving long-term administration of indometacin.

- *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:*
  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 indometacin, the treatment should be withdrawn. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

- 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).
- NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), pre-existing sigmoid lesions (such as diverticulum or carcinoma), or the development of these conditions, as these conditions may be exacerbated (see section 4.8).
- Caution is advised in patients with pre-existing sigmoid lesions (such as diverticulum or carcinoma) or ulcerative colitis or Crohn's disease (or the development of these conditions) as indometacin can aggravate these conditions (see Section 4.8).
- Gastro-intestinal disorders which occur can be reduced by giving indometacin with food, milk or antacids. They usually disappear on reducing the dosage; if not, the risks of continuing therapy should be weighed against the possible benefits.
- Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity ulceration or bleeding, such as oral corticoseroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
- 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.

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

- *Impaired female fertility:*
  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.

- *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, and any other sign of hypersensitivity.

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

- 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 infectious disease and this should be borne in mind in order to avoid delay in starting treatment for infections. Indometacin should be used with caution in patients with an existing, albeit controlled infection. Caution is advised with concomitant use of live vaccines.

- 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.

- 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.

- 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.

- 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 headaches 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.

- Patients with rare hereditary problems of fructose or galactose intolerance, total lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

- 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.

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). 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, co-administration of aspirin may decrease the blood concentration of indometacin.
- 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. Skin reactions and neurotoxicity have been reported with ciprofloxacin.
- Anti-coagulants: Although clinical studies suggest that indometacin does not influence the hypoprothrombinaemia induced by anticoagulants, patients also receiving anticoagulants should be closely observed for alterations of the prothrombin time. The risk of ulceration and bleeding is increased with indometacin (see section 4.4).Antidiabetics: the effect of sulphonylureas may be increased by NSAIDs. Isolated case of metabolic acidosis with metformin.
- Antiepileptics: effect of phenytoin possibly increased by NSAIDs.
- Anti-hypertensives: 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, diuretics, hydralazine, nifedipine or losartan. Hyperkalaemia has also been reported with ACE inhibitors.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4) Increased risk of bleeding with clopidogrel. 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: pharmacokinetic changes have been recorded with zalcitabine/indometacin. Risk of indometacin toxicity with ritonavir, avoid concomitant use.
  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.
- Benzodiazepines: increased risk of dizziness with diazepam and indometacin.
- Cardiac Glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR, and increase plasma glycoside levels. Indometacin given concomitantly with digoxin

has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indometacin and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

- 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: caution should be employed in use with cyclophosphamide as acute water intoxication has been reported.
- 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 occurs. 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 antihypertensive 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; indometacin 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. Simultaneous use should be undertaken with caution.
- 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.
- Muromonab-CD3: significant rise in incidence of psychosis and encephalopathy in patients receiving both these drugs.
- Indometacin and potassium-sparing diuretics each may be associated with increased plasma potassium levels. The potential effects of Indometacin and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.
- Pentoxifylline: Possible increased risk of bleeding when taken with NSAIDs.

- Phenylpropanolamine: Hypertensive crises have been reported due to oral phenylpropanolamine alone and, rarely, to phenylpropanolamine given with indometacin. This additive effect is probably due partly to indometacin's inhibition of prostaglandin synthesis. Caution should be exercised when indometacin and phenylpropanolamine are administered concomitantly.
- 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.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
- Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Tiludronic acid: bisphosphonates bioavailability increased by indometacin.
- Triamterene: indometacin and triamterene should not be administered together since reversible renal failure may be induced.
- Vasodilators: possible increased risk of bleeding with NSAIDs.

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 (see above);

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).

Breast-feeding:
Administration of Indometacin is not recommended in breast-feeding mothers. Indomethacin is excreted in breast milk

Fertility:
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.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

• *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 patients manifest anaemia secondary to obvious or occult gastro-intestinal bleeding, appropriate blood determinations are recommended. Epistaxis has been reported rarely.
• *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 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 lightheadedness 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, 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 therapy**.**

• *Eye disorders:* 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:* There have been reports of hypotension, tachycardia, chest pain, arrhythmia, palpitations.

• *Cardiovascular and cerebrovascular:*

Oedema hypertension and cardiac failure have been reported in association with NSAID treatment.• *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.

• *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 bstruction), with suppositories, tenesmus and irritation of the rectal mucosa have occasionally been reported, bleeding (even without obvious ulceration or from a diverticulum) and perforation of preexisting sigmoid lesions (such as diverticulum or carcinoma), increased abdominal pain or exacerbation of the condition in patients with ulcerative colitis or Cohn’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. Gastro-intestinal 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 has been observed. Pancreatitis has been reported very rarely.

• *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.
• *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.
• *Renal and urinary disorders:* haematuria, nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure, renal insufficiency, proteinuria including renal failure (all rare), blood urea elevation, and haematuria (all infrequent).. 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
• 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).

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.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation or lethargy, mental confusion, excitation, coma, drowsiness, dizziness, tinnitus, fainting, paraesthesia, numbness, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Treatment: patients should be treated symptomatically as required. The stomach should be emptied as quickly as possible if the ingestion is recent and correction of severe electrolyte abnormalities may need to be considered. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. 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. Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastro-interstinal ulceration and haemorrhage have been reported as adverse reactions of indometacin. Use of antacids may be helpful.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.

It can be noted that indometacin has biphasic plasma elimination with the terminal phase showing a half-life ranging between 2.6 and 11.2 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M01A B01

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

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: The formulation has a gradual in vitro release profile over 8 hours. Absorption is slowed but remains virtually complete when taken with 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.

Metabolism: It is metabolised in the liver primarily by demethylation and deacetylation, it also undergoes glucuronidation and enterohepatic circulation. Half-life is between 3 – 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.

The following pharmacokinetic particulars were obtained with indometacin MR 75mg Capsules; (n=8)

t½∞	3.999 hours
t½β	3.853 hours
Tmax	6.182 hours
Cmax	2.192 µg/ml
AUC0-24	31.190 µg/ml/hours

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains: sucrose, corn starch, lactose, povidone, talc, magnesium stearate, polymers of methacrylic acid, acrylic acid esters and methacrylic acid esters.

Capsule shell: titanium dioxide (E171), erythrosine (E127), indigotine (E132), yellow iron oxide (E172) and gelatin.

Printing ink: shellac glaze, titanium dioxide (E171) and iron oxide black E172).

6.2 Incompatibilities

See under interactions with other medicaments and other forms of interaction section.

6.3 Shelf life

Shelf-life
In the medicinal product as packaged for sale: 36 months

Shelf-life after dilution/reconstitution
Not applicable

Shelf-life after first opening
Not applicable

6.4 Special precautions for storage

Store in a dry place below 25ºC

Protect from light

6.5 Nature and contents of container

Capsule container: polypropylene securitainer with polyethylene closure
Number of capsules per container: 28 or 100

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0436

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/1997 / 18/03/2009

10 DATE OF REVISION OF THE TEXT

03/02/2023