1 NAME OF THE MEDICINAL PRODUCT

Indocid Capsules 25 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indocid Capsules 25 mg contain 25 mg of indometacin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Indocid Capsules 25 mg are ivory, opaque capsules marked 'MSD 25'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-steroidal anti-inflammatory agent indicated for the active stages of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, degenerative joint disease of the hip, low-back pain, and acute gouty arthritis.

Also indicated in inflammation, pain and oedema following orthopaedic procedures; and the treatment of pain and associated symptoms of primary dysmenorrhoea.

4.2 Posology and method of administration

The dosage of indometacin should be carefully adjusted to suit the needs of the individual patient.

Posology
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.

In order to reduce the possibility of gastro-intestinal disturbances, indometacin capsules should always be taken with food or an antacid.

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.

Chronic conditions

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.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- History of peptic ulcer or active peptic ulcer
- Recurrent history of gastro-intestinal lesions
- In patients who have nasal polyps associated with angioneurotic oedema, who show sensitivity to indometacin or any of the ingredients in this product, or who have experienced acute asthmatic attacks, urticaria or rhinitis as a result of therapy with aspirin or other non-steroidal anti-inflammatory drugs
- During the third trimester of pregnancy or lactation (see section 4.6)

4.4 Special warnings and precautions for use

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.

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.

Indometacin should be used cautiously in patients with a history of bronchial asthma and in patients with psychiatric disorders, epilepsy, or Parkinsonism, as indometacin may tend to aggravate these disorders.

NSAIDs should only be given with care to patients with a history of gastro-intestinal disease.

Gastro-intestinal disturbances may be minimised by giving indometacin orally with food or an antacid. They usually disappear on reducing the dosage; if not, the risks of continuing therapy should be weighed against the possible benefits. If gastro-intestinal bleeding does occur, indometacin should immediately be discontinued.

Single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small or large intestine, have been reported to occur with indometacin. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Gastro-intestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

Fluid retention and peripheral oedema have been observed in some patients taking indometacin. Indometacin should therefore be used with caution in patients with cardiac dysfunction, hypertension or other conditions predisposing to fluid retention.

Indometacin may mask the signs and symptoms of infection. Indometacin should be used with caution in patients with existing but controlled infection.

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. Discontinue therapy if eye changes are observed.

Patients should be periodically observed to allow early detection of any unwanted effects on peripheral blood (anaemia), liver function, or gastro-intestinal tract.

Indometacin can inhibit platelet aggregation. This effect usually disappears within 24 hours of discontinuing indometacin. Bleeding time is prolonged (but within normal range) in normal adults. Because this effect may be exaggerated in patients with underlying haemostatic defects, indometacin should be used cautiously in patients with coagulation defects.

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.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a non-steroidal anti-inflammatory agent may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. A non-steroidal anti-inflammatory drug should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

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 (see 4.5 ‘Interaction with other medicaments and other forms of interaction’).

Since indometacin is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be used to avoid excessive drug accumulation.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin: the use of indometacin with aspirin or other salicylates is not recommended. Controlled clinical studies have shown no enhanced therapeutic effect, and one study showed a significant increase in the incidence of gastro-intestinal side effects. A study in normal volunteers showed that chronic administration of 3.6 g aspirin with indometacin lowered the indometacin blood levels by approximately 20%.

Diflunisal: co-administration of diflunisal with indometacin increases the plasma level of indometacin by about a third, with a concomitant decrease in renal clearance. Fatal gastro-intestinal haemorrhage has occurred. The combination should not be used.

Other NSAIDS: the concomitant use of indometacin with other NSAIDs is not recommended due to the increased possibility of gastro-intestinal toxicity, with little or no increase in efficacy.

Anticoagulants: 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.

Probenecid: co-administration of probenecid may increase plasma levels of indometacin.

Methotrexate: caution should be exercised with simultaneous use of indometacin with methotrexate. Indometacin has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Cyclosporin: administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporin has been associated with an increase in cyclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporin, and renal function should be monitored carefully.

Lithium: indometacin 50 mg three times a day produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady-state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when indometacin and lithium are given concomitantly, the patient should be observed carefully for signs of lithium toxicity. In addition, the frequency of monitoring serum lithium concentrations should be increased at the outset of such combination drug treatment.

Diuretics: in some patients, the administration of indometacin can reduce the diuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when indometacin and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Indometacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by frusemide 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 indometacin resulted in reversible acute renal failure in two of four healthy volunteers. Indometacin and triamterene should not be administered together.

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.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indometacin.

Cardiac glycosides/Digoxin: 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.

Antihypertensive medications: co-administration of indometacin and some antihypertensive agents may attenuate acutely the hypotensive effect of the latter, due partly to indometacin's inhibition of prostaglandin synthesis. 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, diuretics, hydralazine, or losartan (an angiotensin II receptor antagonist).

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.

Corticosteroids: the risk of gastro-intestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids.

Mifepristone: NSAIDs and aspirin should be avoided until at least 8 to 12 days after administration of mifepristone.

Quinolone antibiotics: there have been reports that 4-quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them.

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 and gastroschisis 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 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.

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 oligo-hydroamniosis;

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.

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

Breast-feeding
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

Patients should be warned that they may experience dizziness, drowsiness, visual disturbances or headaches and if they do, should not drive or undertake activities requiring alertness.

4.8 Undesirable effects

CNS reactions - headaches, dizziness, light-headedness, depression, vertigo, and fatigue (including malaise and listlessness). Reactions reported infrequently include mental confusion, anxiety, syncope, drowsiness, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscle movements, insomnia, psychiatric disturbances such as hallucinations, depersonalisation; and, rarely, paraesthesia, dysarthria, aggravation of epilepsy and Parkinsonism. These are often transient and disappear frequently with continued treatment or with reduced dosage. However, occasionally, severe reactions require stopping therapy.

Gastro-intestinal - the more frequent reactions are nausea, anorexia, vomiting, epigastric distress, abdominal pain, constipation, and diarrhoea. Others which may develop are ulceration - single or multiple - of oesophagus, stomach, duodenum or small or large intestine, including perforation and haemorrhage with a few fatalities having been reported; gastro-intestinal tract bleeding without obvious ulcer formation; and increased abdominal pain when used in patients with pre-existing ulcerative colitis. Reactions occurring infrequently are stomatitis; gastritis; flatulence; bleeding from the sigmoid colon - occult or from a diverticulum - and perforation of pre-existing sigmoid lesions (diverticula, carcinoma). Rarely, intestinal strictures (diaphragms) and intestinal ulceration followed by stenosis and obstruction has been reported. With suppositories, tenesmus and irritation of the rectal mucosa have occasionally been reported. Pancreatitis has been reported with an unknown frequency. Other gastro-intestinal side effects which may or may not be caused by indometacin include: ulcerative colitis and regional ileitis.

Hepatic - rarely, hepatitis and jaundice. (Some fatalities reported.)

Cardiovascular/Renal - oedema, increased blood pressure, tachycardia, chest pain, arrhythmia, palpitation, hypotension, congestive heart failure, blood urea elevation, and haematuria (all infrequent).

Dermatological/Hypersensitivity - pruritus, urticaria, angioneurotic oedema, angiitis, erythema nodosum, skin rash and photosensitivity, exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, loss of hair, rapid fall in blood pressure resembling a shock-like state, acute anaphylaxis, acute respiratory distress including sudden dyspnoea, asthma and pulmonary oedema (all infrequent). Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Haematological - infrequently, blood dyscrasias may occur, including leucopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia, agranulocytosis, bone-marrow depression, disseminated intravascular coagulation, and particularly thrombocytopenia. Because some patients may develop anaemia secondary to obvious or occult gastro-intestinal bleeding, appropriate blood determinations are recommended.

Ocular - infrequently, blurred vision, diplopia, and orbital and peri-orbital pain. Corneal deposits and retinal disturbances, including those of the macula, have been reported in patients with rheumatoid arthritis on prolonged therapy, but similar changes may also be expected in patients with rheumatoid arthritis who have not received indometacin.

Aural - tinnitus, hearing disturbances (rarely deafness).

Genito-urinary - proteinuria, nephrotic syndrome, interstitial nephritis, and renal insufficiency including renal failure (all rare).

Miscellaneous - vaginal bleeding, hyperglycaemia, glycosuria, hyperkalaemia, flushing and sweating, epistaxis, breast changes including enlargement and tenderness, gynaecomastia, and ulcerative stomatitis (all rare).

Laboratory tests
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 non-steroidal anti-inflammatory drugs 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.

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.

<u>Reporting of suspected adverse reactions</u>
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
The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paraesthesia, numbness, and convulsions.

Management
Treatment is symptomatic and supportive. 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. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given. 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-intestinal ulceration and haemorrhage have been reported as adverse reactions of indometacin. Use of antacids may be helpful.

The plasma elimination of indometacin is biphasic with the half-life of the terminal plasma half-life phase between 2.6 and 11.2 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and Antirheumatic Products, Non-Steroids, ATC code: M01AB01

Indometacin has anti-inflammatory, antipyretic, and analgesic effects, it is an inhibitor of prostaglandin synthetase.

5.2 Pharmacokinetic properties

Indometacin is rapidly and almost completely absorbed on oral administration, and peak plasma levels are reached in ½ to 2 hours. Absorption is slowed but remains virtually complete when taken with food. About 90% is bound to plasma proteins. It appears to undergo enterohepatic cycling. It is metabolised partly by O-demethylation, partly by N-deacylation, and unchanged drug and metabolites are partly conjugated with glucoronic acid, in man, it is excreted unchanged and as it metabolites in both urine and faeces.

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

Colloidal silicon dioxide, lactose, liquid lecithin concentrate, and magnesium stearate E572. *Capsule shells*: gelatin, titanium dioxide E171 and yellow ferric oxide E172.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C. Keep in original package.

6.5 Nature and contents of container

Indometacin Capsules 25 mg: high density bottles with high density polyethylene cap-to-cap closures containing 100 or 500 capsules. Opaque 250 micron PVC blisters with 20 micron aluminium lid. Each blister contains 10 capsules. Each pack contains 90 capsules.

6.6 Special precautions for disposal and other handling

Indometacin Capsules should always be taken with food or an antacid.

7. MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive

Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 39699/012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 June 1981

10 DATE OF REVISION OF THE TEXT

27/05/2021