

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indometacin Capsules BP 25mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indometacin BP 25.00mg

3 PHARMACEUTICAL FORM

Capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indometacin is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and other rheumatic disorders. It is indicated in the treatment of acute gout.

Indometacin is 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

Route of administration: Oral

Recommended Dose and Dosage Schedules:

The usual dose is:-

Adults:

50-100mg increasing to 150-200mg daily in divided doses.

Elderly patients:

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:

Contra-indicated, as paediatric dosage is not established.

To be taken preferably with or after food.

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

4.3 Contraindications

Contraindicated in children as a paediatric dose has not been established.

Contraindicated in patients with an active peptic ulcer, gastro intestinal ulceration or bleeding, a recurrent history of gastro-intestinal lesions, renal disease, psychiatric disorders, epilepsy or parkinsonism.

Hypersensitivity to any of the constituents.

NSAID's 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. Severe hepatic, renal and cardiac failure (See section 4.4 – Special warnings and precautions for use).

During the last trimester of pregnancy (See section 4.6 – Pregnancy and lactation).

Active or previous peptic ulcer.

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 Interactions).

Severe heart failure.

4.4 Special warnings and precautions for use

Concurrent administration of Aspirin or other NSAID's should be avoided as the incidence of side effects are enhanced without additional therapeutic benefit.

Indometacin should be administered with caution to patients with impaired hepatic or cardiac function and to those with bleeding disorders, epilepsy, parkinsonism or psychiatric disorders.

Use with caution in patients with conditions predisposing to fluid retention e.g. cardiac dysfunction and hypertension. Fluid retention may occur, rarely precipitating congestive heart failure in elderly patients.

Elderly patients may be especially susceptible to the toxic effects of Indometacin.

Use with caution in patients with existing but controlled infection as Indometacin may mask the signs and symptoms of infection. May impair ability to drive or operate machinery. In chronic rheumatoid disease ophthalmological examinations at periodic intervals are recommended. Patients should be periodically observed to allow early detection of any unwanted side effects on peripheral blood (anaemia). Use cautiously in patients with coagulation defects as bleeding time may be prolonged. False negative results in the dexamethasone suppression test (DST) in patients treated with Indometacin have been reported.

In all patients:

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAID's especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2 – Posology and administration).

Respiratory disorders:

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

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greater risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (See also section 4.3 – Contraindications).

Caution in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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 a previous history of serious GI events.

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.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrototoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5 – Interactions).

When GI bleeding or ulceration occurs in patients receiving Indometacin, the treatment should be withdrawn.

NSAID's should 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 – Undesirable effects).

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 – Undesirable effects).

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.

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).

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).

4.5 Interaction with other medicinal products and other forms of interaction

Indometacin may cause blocking of the Furosemide-induced increase in plasma renin activity.

The risk of hyperkalaemia may be increased when used with potassium sparing diuretics. There have been occasional reports of decreased renal function when Indometacin was given with triamterene.

Probenecid delays excretion of Indometacin and increases the risk of toxicity. Co-administration of Diflunisal increases the plasma level of Indometacin by about a third with concomitant decrease in renal clearance. Fatal gastrointestinal haemorrhage has occurred. The combination should not be used.

Other analgesics: Avoid concomitant use of two or more NSAID's (including aspirin) as this may increase the risk of adverse effects (see section 4.3 Contraindications).

Anti-hypertensives: Reduced anti-hypertensive effect.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of GI bleeding (See section 4.4 Special warnings and precautions for use).

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4 Special warnings and precautions for use).

Quinolone antibiotics: Animal data indicate that NSAID's can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAID's and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

4.6 Pregnancy and lactation

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (See section 4.3 – Contraindications). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

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

See Section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The commonest adverse effects occurring with Indometacin are gastrointestinal disturbances (including diarrhoea, nausea and abdominal pain),

headache and dizziness.

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (See section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4 Special warnings and precautions for use), have been reported following administration. Less frequently, gastritis has been observed.

Hypersensitivity: Hypersensitivity reactions (including angio-oedema and bronchospasm) have been reported following treatment with NSAID's. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritis, urticaria, purpura, angioedema and, more rarely exfoliative and bullous dermatoses (including toxic epidermal necrolysis, erythema multiforme).

Cardiovascular: Oedema has been reported in association with NSAID treatment.

Other adverse events reported less commonly include:

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, renal failure and papillary necrosis.

Hepatic: abnormal liver function, hepatitis and jaundice.

Neurological and special senses: Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (See section 4.4) depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia, leucopenia and purpura.

Dematological: photosensitivity.

Other adverse effects include light headedness, insomnia, psychiatric disturbances, syncope, convulsions, coma, blurred vision and other ocular effects, oedema, weight gain, hypertension, haematuria, Stevens Johnson syndrome and alopecia.

Epistaxis, hyperglycaemia, hyperkalaemia and vaginal bleeding have been reported.

Hypersensitivity reactions may also occur in Aspirin-sensitive patients.

Indometacin may provoke or worsen asthma.

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

Clinical trial and epidemiological data suggest that 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).

4.9 Overdose

(a) Symptoms

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

(b) Therapeutic measure

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion 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

Indometacin is a non-steroidal anti-inflammatory agent with analgesic and anti-pyretic properties. It inhibits prostaglandin synthesis. It has the property of stabilising the lysosome membrane rendering it less susceptible to breakdown and this may contribute to its anti-inflammatory activity.

5.2 Pharmacokinetic properties

Indometacin is readily absorbed from the gastro-intestinal tract; peak plasma concentrations are reached one half to two hours after a dose. More than 90% is bound to plasma proteins. It is metabolised in the liver and kidneys and is excreted in the urine, mainly as the glucuronide, and to a much lesser extent in the faeces. Indometacin is also excreted in milk.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose 110# BP
Starch (Maize) BP
Silicon Dioxide USP
Magnesium Stearate (E572) BP
Capsule shell components:
Erythrosine (E127)
Quinoline Yellow (E104)
Titanium Dioxide (E171)

6.2 Incompatibilities

None stated

6.3 Shelf life

3 years - Polypropylene containers
2 years - Blister strips

6.4 Special precautions for storage

Keep tightly closed, in a dry place at or below 25 °C.

6.5 Nature and contents of container

White polypropylene container with tamper evident closure.

1000, 500, 100, 84, 70, 56, 42, 28, 21, 15 and 14 capsules.
Blister strips: 84, 70, 56, 42, 28, 21, 15 and 14 capsules.

6.6 Special precautions for disposal

Nothing stated.

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower, 12-16 Addiscombe Road
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8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0425

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/10/87 / 05/02/98

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

**12 INSTRUCTIONS FOR PREPARATION OF
RADIOPHARMACEUTICALS (IF APPLICABLE)**