

CTD MODULE 1
ADMINISTRATIVE INFORMATION AND
PRODUCT INFORMATION

Product Name :	INDOREN CAPSULES (Indomethacin BP 25 mg)
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1.5 Product Information: INDOREN CAPSULES

1.5.1 Prescribing information (Summary of products characteristics):

1. Name of the Medicinal Product: INDOREN CAPSULES

Strength:

Each hard gelatin capsules contains Indomethacin BP 25 mg

Pharmaceutical form: Capsules

2. Qualitative and Quantitative composition:

Qualitative composition and Quantitative composition:

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)			
		Each hard gelatin capsules contains Indomethacin BP 25 mg			
		Quantity in mg per capsule	%	Quantity in Kg Per 1,000,000 C	%
Contents of INDOREN CAPSULES					
Indomethacin	Active	25.000	14.28	25.000	14.28
Maize starch	Binder	30.000	17.14	30.000	17.14
Microcrystalline cellulose	Diluent	110.000	62.86	110.000	62.86
Purified talc	Dusting powder	5.000	2.86	5.000	2.86
Sodium starch glycollate	Glidant	5.000	2.86	5.000	2.86
EHG (Indoren capsules)	Vehicle	1 Unit	-	1,000,000 Nos.	-
Total	NA	175.00	100.00	175.00	100.00

3. Pharmaceutical form: Capsules

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4. Clinical particular's:

4.1 Therapeutic indication:

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, gout and lumbago.
- inflammation, pain and oedema following orthopaedic procedures.
- treatment of pain and associated symptoms of primary dysmenorrhoea.

Since indometacin is not a simple analgesic, its use should be limited to the above conditions.

4.2 Posology and method of administration:

Posology

The dosage should be carefully adjusted according to the needs of the individual patient, starting with a low dose.

To reduce the possibility of gastro-intestinal disturbances, indometacin capsules should always be taken with food, milk or immediately after meals, or with an antacid and in chronic conditions start the therapy with a low dosage, increasing as required.

Adults: The recommended oral dosage range is 50-200mg daily.

Acute rheumatoid arthritis: Initially 25mg two or three times a day.

Chronic rheumatic disorders: 25mg two or three times daily. (If response is inadequate, gradually increase by 25mg. Adequate response is usually achieved with not more than 150mg daily, rarely more than 200mg daily).

Sudden flare up of chronic condition: Increase if necessary, by 25mg daily until a satisfactory response is obtained, or a dosage of 150-200mg daily is reached. (If this causes any adverse effects, it should be reduced to a tolerable level for two or three days, then carefully increased, as tolerated).

Acute musculoskeletal disorders: Initially 50mg two or three times daily, according to severity for 10-14 days. Normally 150mg daily, rarely 200mg daily.

Lumbago: 50mg two or three times daily, according to severity. Duration of treatment is not normally more than five days, but may be continued for up to 10 days.

Gout: Acute attack: 50mg three or four times daily until symptoms subside.

Following orthopaedic procedures: Normally 100-150mg daily in divided doses until symptoms subside.

Additional considerations: In conditions where patients require a dosage of 150-200mg a day, it is often possible to reduce this gradually to a maintenance level of 75-100mg a day. In patients with persistent night pain and/or morning stiffness, a dose of up to 100mg at bed time may be helpful in affording relief. It is rarely necessary to exceed a dosage of 200mg a day.

Dysmenorrhoea: Up to 75mg daily, starting with onset of cramps or bleeding, and continuing for as long as symptoms usually last.

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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: Indometacin is contraindicated in children as its safety has not been established.

Method of Administration: Oral route.

4.3 Contraindication:

NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (eg asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

- Hypersensitivity to indometacin or to any of the excipients.
- Severe heart failure, hepatic failure and renal failure.
- Not to be used in patients who have nasal polyps
- During the last trimester of pregnancy or lactation.
- Safety in children has not been established.
- 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.

4.4 Special warning and precaution for use:

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

- The use of Indometacin capsules with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided
- 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).

- 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.

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- 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.
- Indometacin may mask the signs and symptoms of infection, so antibiotic therapy should be initiated promptly if an infection occurs during therapy with indometacin. It should be used 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 are 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, 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. 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 a NSAID may precipitate overt renal decompensation. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, the elderly, diabetes mellitus, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. Indometacin should be given with caution and renal function should be monitored in these patients.

Discontinuation of NSAID 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.

- 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:

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.

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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 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

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 .

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

• 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

• 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.

• 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.

• 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.

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- 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. 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 capsules should be discontinued at the first appearance of skin rash, mucosal lesions, and 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.

4.5 Interactions with other medicinal products and other forms of interactions:

- 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
- Antacids: the bioavailability of indometacin may be reduced by concomitant antacid therapy.
- Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin
- Antidepressants (SSRI): increased risk of bleeding
- Antidiabetics: the effect of sulfonylureas may be increased by NSAIDs.
- Antihypertensives: 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, hydralazine or nifedipine. An increased risk of hyperkalaemia has also been reported when NSAIDs are taken with ACE inhibitors.
- 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
- 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-cardiac glycoside levels.
- Ciclosporin: Increased risk of nephrotoxicity. Administration of NSAIDs concomitantly with ciclosporin has been associated with an increase in ciclosporin-

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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 gastro-intestinal 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 levels of indometacin by about a third with a concomitant decrease in renal clearance. 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.
- 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 indometacin plasma levels. 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 the NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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- Salicylates: 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.
- 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 indomethacin 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.

Additional information on special populations:

Not Applicable

Pediatric population:

Not Applicable

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. 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

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Consequently indometacin is contraindicated during the third trimester of pregnancy.

Breast-feeding:

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

4.7 Effects on ability to drive and use machines:

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:

Blood and lymphatic system 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.

- Immune system disorders:: 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: 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 rheumatoid arthritis on prolonged therapy with indometacin. Ophthalmic examinations are desirable in patients given prolonged treatment.

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- Ear and labyrinth disorders: tinnitus or hearing disturbances (rarely deafness) have been reported.
- Cardiac disorders: oedema, hypertension, hypotension, tachycardia, chest pain, arrhythmia, palpitations, syncope and cardiac failure have been reported.
- 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)
- 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.
- 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 preexisting sigmoid lesions (such as diverticulum or carcinoma), increased abdominal pain or exacerbation of the condition in patients with ulcerative colitis or Crohns 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.
- Hepatobiliary 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, photosensitivity, erythema nodosum, rash and exfoliative dermatitis, bullous reactions including Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrolysis (very rare), hair loss, sweating and exacerbation of psoriasis.
- Musculo-skeletal and connective tissue 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 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
- Reproductive system and breast disorders: vaginal bleeding, breast changes (enlargement, tenderness, gynaecomastia).

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4.9 Overdose and Treatment:

a) 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.

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.

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5. Pharmacological Properties:

5.1 Pharmacodynamic properties:

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 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 levels occur in 0.5-2 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:

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

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6. Pharmaceutical Particulars:

6.1 List of excipients

Indoren Capsules contains the following excipients:

Maize starch, Microcrystalline cellulose, Purified talc, Sodium starch glycollate.

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precaution for storage

Store in cool & dry place. Below 25°C.

6.5 Nature and contents of container

Alu/PVC blister

6.6 Special precautions for disposal

No special precaution.

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7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Marketing Authorization Holder:
Rene Industries Ltd

Address : PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

Manufactured by:

Rene Industries Ltd

Address : PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

8. MARKETING AUTHORISATION NUMBER:

Not Applicable

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

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable

11. DOSIMETRY (IF APPLICABLE):

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable