SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ENDOL® 25 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Indomethacin (micronized) 25 mg

Excipient(s):

Lactose monohydrate 80 mg

Sodium lauryl sulfate 1.5 mg

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule

Homogeneous powder contained in hard gelatin capsules with an opaque light blue body and an opaque dark blue cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as for the management of acute gouty arthritis, acute musculoskeletal pain, postoperative pain, and dysmenorrhoea.

4.2 Posology and route of administration

Posology/frequency and duration of administration:

The dosage of ENDOL should be individually and carefully adjusted to suit the patient's needs.

To reduce the likelihood of gastrointestinal discomfort, ENDOL capsules should always be taken with food or an antacid.

For chronic conditions, the best results with minimal side effects will be achieved by starting treatment with a low dose, gradually increasing it as required, and continuing the therapy for a

sufficient period (up to one month in some cases). The recommended oral dose range is 50 mg to 200 mg daily in divided doses.

Dosage for dysmenorrhoea: Up to 75 mg daily, starting at the onset of cramps or bleeding and continuing for as long as symptoms persist.

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

Method of administration:

ENDOL capsules are for oral use and should be swallowed whole with a glass of water.

Additional information on special populations:

Kidney/Liver failure:

It should not be used in cases of severe kidney and liver failure.

Pediatric population:

Safety in children has not been established. A paediatric dose has not been determined.

Geriatric population:

ENDOL should be used with caution in elderly patients, who are more prone to adverse reactions.

4.3 Contraindications

Contraindicated in patients with hypersensitivity to indomethacin or any of the excipients of this medicine; in patients with a history of peptic ulcer or active peptic ulcer, a history of recurrent gastrointestinal lesions, or nasal polyps associated with angioneurotic oedema; and in patients who have experienced acute asthmatic attacks, urticaria, or rhinitis after treatment with aspirin or other non-steroidal anti-inflammatory drugs. Severe, rarely fatal, anaphylaxis-like reactions to NSAIDs have been reported in such patients. (See section 4.4 Special warnings and precautions for use).

Safety in children has not been established.

ENDOL should not be used during pregnancy or lactation (see section 4.6 'Pregnancy and lactation').

For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (See section 4.4 Special warnings and precautions for use).

Severe liver failure.

Severe kidney failure.

Severe heart failure.

Gastrointestinal bleeding, cerebrovascular bleeding, and other bleeding disorders.

Contraindicated in patients with a history of gastrointestinal bleeding or perforation related to previous NSAID therapy.

4.4 Special warnings and precautions for use

Cardiovascular thrombotic events:

Clinical trials of several selective and non-selective COX-2 inhibitors of up to three years duration have shown an increased risk of serious, potentially fatal, cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. All NSAIDs, both selective and non-selective COX-2 inhibitors, may carry a similar risk. Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimise the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if they occur.

There is no consistent evidence that concomitant use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use. The concomitant use of NSAIDs with aspirin increases the risk of serious GI events.

There are insufficient data to rule out such a risk for indomethacin.

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with indomethacin after careful consideration. A similar consideration should be made before initiating long-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Two large, controlled clinical trials of a selective COX-2 NSAID for the treatment of pain in the first 10-14 days following CABG surgery have shown an increased incidence of myocardial infarction and stroke (See Section 4.3 Contraindications).

Hypertension:

As with all other NSAIDs, indomethacin can lead to the onset of new hypertension or the worsening of pre-existing hypertension, either of which may contribute to the increased risk

of cardiovascular events. Patients treated with thiazide or loop diuretics may have an impaired response to diuretic therapy when taking NSAIDs. NSAIDs, including indomethacin, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely at the start of indomethacin treatment and throughout the course of therapy.

Congestive Heart Failure and Oedema:

Fluid retention and oedema have been observed in some patients treated with NSAIDs, including indomethacin. Therefore, indomethacin should be used with caution in patients with fluid retention or heart failure.

Headache, sometimes accompanied by dizziness and light-headedness, may occur, usually in the early stages of treatment. Starting therapy with a low dose and gradually increasing it will generally reduce the incidence of headache. These symptoms will often disappear with the continuation of therapy or with a reduction in dosage; however, if the headache persists despite reducing the dose, ENDOL should be discontinued. Patients should be warned that they may experience dizziness, and if they do, they should not drive a car or engage in potentially hazardous activities that require alertness.

ENDOL should be used with caution in patients with a history of bronchial asthma and in patients with psychiatric disorders, epilepsy, or parkinsonism, as indomethacin may worsen these conditions.

Non-steroidal anti-inflammatory agents should be given with caution to patients with a history of gastrointestinal disease.

Gastrointestinal discomfort can be minimised by administering ENDOL orally with food or an antacid. Symptoms often disappear with a reduction in dose; if they do not, the potential benefits should be weighed against the possible risks of continuing treatment. If gastrointestinal bleeding occurs, ENDOL should be discontinued immediately.

Single or multiple ulcers, including perforation and haemorrhage of the oesophagus, stomach, duodenum, or small or large intestine, have been reported with ENDOL. Fatalities have been reported in some cases. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Gastrointestinal bleeding has occurred without obvious ulcer formation and without perforation of pre-existing sigmoid lesions (e.g., diverticulum, carcinoma, etc.). Rarely, increased abdominal pain in patients with ulcerative colitis, or the development of ulcerative colitis and regional ileitis, has been reported. NSAIDs should be prescribed with extreme

caution to patients with a prior history of ulcer disease or GI bleeding (See Section 4.3 Contraindications) and to the elderly. Studies have shown that patients with a prior history of peptic ulcer and/or GI bleeding who use NSAIDs have a 10-fold greater risk of developing GI bleeding compared to patients without these risk factors. Other factors that may increase the risk of GI bleeding in patients treated with NSAIDs include: treatment with oral corticosteroids, treatment with anticoagulants, prolonged therapy with NSAIDs, smoking, alcohol use, advanced age, and poor general health status. Most spontaneous reports of fatal GI events have been in elderly and debilitated patients; therefore, particular caution should be- exercised when treating this population.

To minimise the potential risk of an adverse GI event, patients should be treated with the lowest effective NSAID dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy, and if a serious GI event is suspected, an additional evaluation and treatment should be initiated immediately. NSAID therapy should be discontinued if the serious adverse event does not resolve. For high-risk patients, alternative therapies that do not involve NSAIDs should be considered.

Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding), particularly in the initial stages of treatment. Caution should be advised for patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants like warfarin, selective serotonin-reuptake inhibitors, or antiplatelet agents such as acetylsalicylic acid (see Section 4.5 Drug Interactions and Other Interactions).

Indomethacin should be given with caution to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) (See Section 4.8. Undesirable Effects).

The frequency of adverse reactions associated with NSAIDs, particularly gastrointestinal bleeding and perforation which can be fatal, is increased in elderly patients (See Section 4.3. Contraindications).

Fluid retention and peripheral oedema have been observed in some patients receiving ENDOL. Therefore, ENDOL should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions that predispose to fluid retention.

Gastrointestinal discomfort can be minimised by administering ENDOL orally with food or an antacid. These discomforts often disappear with a reduction in dose; if they do not, the

potential benefits should be weighed against the possible risks of continuing treatment. If gastrointestinal bleeding occurs, ENDOL should be discontinued immediately.

Tenesmus and irritation of the rectal mucosa have occasionally been reported with ENDOL suppositories.

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

In patients with rheumatoid arthritis, ocular changes may occur which can be associated with the underlying disease or with therapy. Therefore, in chronic rheumatoid disease, ophthalmological examinations at regular intervals are recommended. If ocular changes are observed, discontinue treatment.

To permit early detection of any adverse effects on peripheral blood (anaemia), liver function, or the gastrointestinal tract, patients should be observed regularly.

ENDOL can inhibit platelet aggregation. This effect usually disappears within 24 hours following the discontinuation of ENDOL. In normal adults, the bleeding time is prolonged (but within the normal range). As this effect may be exaggerated in patients with underlying hemostatic defects, ENDOL should be used with caution in patients with coagulation defects.

As with other non-steroidal anti-inflammatory drugs, acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome has been reported in patients on long-term indomethacin administration.

In patients with reduced renal blood flow, where renal prostaglandins play a major role in maintaining renal perfusion, the 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 those receiving any concomitant nephrotoxic drugs. A non-steroidal anti-inflammatory drug should be given with caution, and renal function should be monitored in patients with reduced renal reserve. Discontinuation of the non-steroidal anti-inflammatory drug is usually followed by recovery to the pre-treatment 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 state of hyporeninemic-hypoaldosteronism (see section 4.5 'Interaction with other medicinal products and other forms of interaction').

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

Renal effects:

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Furthermore, renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. As the maintenance of renal blood flow is dependent on renal prostaglandins, indomethacin therapy should be administered with caution in patients with mild (serum creatinine 150-300 µmol/l) to moderate (serum creatinine 300-700 µmol/l) renal impairment. The administration of an NSAID to patients in this condition can cause a dose-dependent reduction in prostaglandin synthesis and, secondarily, in renal blood flow, which may precipitate renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly. In patients with cardiac impairment and those who have undergone major surgery, renal function should be monitored when diuretics are taken concomitantly with drugs known or suspected to cause renal impairment. If renal function deteriorates during therapy, indomethacin treatment should be discontinued. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Concomitant treatment with NSAIDs and tacrolimus may increase the risk of nephrotoxicity due to a decrease in prostacyclin synthesis in the kidney. Therefore, renal function should be closely monitored in patients receiving combination therapy.

Advanced kidney disease:

There are no findings from controlled studies regarding the use of indomethacin in patients with advanced kidney disease. Therefore, treatment with indomethacin is not recommended in patients with advanced kidney disease. If indomethacin therapy must be initiated, close monitoring of the patient's renal function is advised.

Anaphylactoid reactions:

As with other NSAIDs, anaphylactoid reactions may occur with indomethacin, even in some patients without known prior exposure to the drug. ENDOL should not be given to patients with the "aspirin triad." This symptom complex typically occurs in patients with asthma who have rhinitis with or without nasal polyps, or who experience severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. (See Section 4.3 and Section 4.4 Special

warnings and precautions for use – Pre-existing asthma). In the event of an anaphylactoid reaction, emergency medical help should be sought.

Skin reactions:

Very rare serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported in association with the use of NSAIDs, including indomethacin (See section 4.8). These serious events can occur without warning. Patients should be informed about the signs and symptoms of serious skin reactions, and the use of ENDOL should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pregnancy:

Like other NSAIDs, indomethacin should not be used during the third trimester of pregnancy because it may cause premature closure of the ductus arteriosus (the opening between the two great arteries [aorta and pulmonary artery] emerging from the heart, which is open in the womb and is supposed to close following birth).

Precautions

General:

Indomethacin should not be expected to be a substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to an exacerbation of the disease. In patients on prolonged corticosteroid therapy, their treatment should be tapered slowly if a decision is made to discontinue corticosteroids. Caution is required in postoperative elderly patients. It is recommended to monitor renal and hepatic functions in patients over 65 years of age.

The pharmacological activity of indomethacin in ENDOL in reducing [fever and] inflammation may diminish the utility of diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

The use of indomethacin, like any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or who are undergoing investigation for infertility, withdrawal of indomethacin should be considered.

Hepatic effects:

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including indomethacin. These laboratory abnormalities may progress, may remain

unchanged, or may be transient with continued therapy. Significant elevations (three or more times the upper limit of normal) of ALT or AST have been reported in approximately 1% of patients in clinical trials with NSAIDs. Furthermore, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and liver failure, some of which resulted in death, have also been reported.

Based on regular clinical observation and laboratory evaluations, it should be considered that accumulation of indomethacin (increase in AUC) may occur in patients with hepatic impairment after treatment with daily doses of 12-16 mg. Otherwise, hepatic impairment has not been observed to affect the pharmacokinetic parameters of indomethacin compared to healthy subjects.

If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g., eosinophilia, skin rashes, etc.), treatment with ENDOL should be discontinued and appropriate investigations initiated.

Haematological effects:

Anaemia is sometimes seen in patients taking NSAIDs, including indomethacin. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect on erythropoiesis. Patients on long-term treatment with NSAIDs, including indomethacin, should have their haemoglobin, APTT (Activated Partial Thromboplastin Time), and haematocrit levels checked regularly, even if they exhibit no signs or symptoms of anaemia.

NSAIDs have been shown to inhibit platelet aggregation and prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients with pre-existing coagulation disorders or those receiving anticoagulants, who may be adversely affected by changes in platelet function, should be carefully monitored during ENDOL use.

Concomitant treatment with NSAIDs and heparin in the setting of spinal or epidural anaesthesia increases the risk of a spinal/epidural haematoma (See Section 4.5. Interaction with other medicinal products and other forms of interaction).

Indomethacin reduces platelet aggregation and prolongs bleeding time, and therefore, should be used with caution when administered to patients with an increased bleeding tendency.

Pre-existing asthma:

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been

reported in these aspirin-sensitive patients, ENDOL should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Laboratory Tests:

During long-term treatment with ENDOL (more than 3 months), regular monitoring of liver enzymes, haematology (haemoglobin), and renal function (creatinine) is required as a precautionary measure. Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor patients for signs or symptoms of GI bleeding. Patients on long-term NSAID therapy should have their complete blood count and chemistry profiles checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, if systemic manifestations occur (e.g., eosinophilia, rash, etc.), or if liver function tests are abnormal or worsen, ENDOL treatment should be discontinued.

As with most NSAIDs, occasional increases in serum transaminase activity, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen levels, and other laboratory abnormalities have been reported. If any such abnormality is significant or persists, the administration of indomethacin should be stopped and appropriate investigations should be initiated.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; no sodium-related side effects are expected at this dose.

4.5 Interactions with other medicinal products and other forms of interaction

Aspirin: The use of ENDOL with aspirin or other salicylates is not recommended. When indomethacin is administered with aspirin, its protein binding is reduced, although the clearance of free indomethacin is not altered. Although the clinical significance of this interaction is unknown, as with other NSAIDs, the concomitant administration of indomethacin and aspirin is generally not recommended because it increases the potential for an increased incidence of adverse effects. Controlled clinical studies have shown no increased therapeutic effect, and one study showed a significant increase in the incidence of gastrointestinal side effects. A study in normal volunteers showed that the chronic

administration of 3.6 g of aspirin with indomethacin reduced blood levels of indomethacin by approximately 20%.

Diflunisal: Concomitant administration of ENDOL with diflunisal increases plasma levels of indomethacin by approximately one-third, with a concurrent decrease in renal clearance. Fatal gastrointestinal haemorrhage has occurred. The combination should not be used.

Other non-steroidal anti-inflammatory drugs: The concomitant use of ENDOL with other non-steroidal anti-inflammatory drugs is not recommended due to the increased potential for gastrointestinal toxicity, with little or no increase in efficacy.

Anticoagulants: Although clinical studies have shown that ENDOL does not affect the hypoprothrombinemia caused by anticoagulants, patients receiving anticoagulants should be closely monitored for changes in prothrombin time. The effects of warfarin and NSAIDs on GI bleeding are synergistic; patients who use both drugs together have a higher risk of serious GI bleeding than users of either drug alone. (See Section 4.4 Special warnings and precautions for use). Careful monitoring of INR is required.

Probenecid: Concomitant use with probenecid may increase plasma levels of indomethacin.

Methotrexate: Caution should be exercised with the concomitant use of ENDOL and Methotrexate. ENDOL has been reported to reduce the tubular secretion of Methotrexate and increase its toxicity.

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

Lithium: Indomethacin 50 mg three times a day has produced a clinically significant increase in plasma lithium and a decrease in renal lithium clearance in psychiatric patients and in normal subjects with steady-state plasma lithium concentrations. This effect has been attributed to the inhibition of prostaglandin synthesis. Consequently, when indomethacin and lithium are administered concomitantly, the patient should be carefully observed for signs of lithium toxicity. In addition, the frequency of monitoring serum lithium concentrations should be increased upon initiation of the combination drug therapy.

Diuretics: In some patients, the administration of ENDOL can reduce the diuretic and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when ENDOL and diuretics are administered concomitantly, the patient should be closely observed to determine whether the desired effect of the diuretic has been achieved.

ENDOL reduces basal plasma renin activity (PRA), as well as the PRA increases caused by furosemide administration, salt, or volume depletion. These facts should be taken into account when evaluating plasma renin activity in hypertensive patients. Clinical studies and post-marketing observations have shown that the use of indomethacin can reduce the natriuretic effect of furosemide and thiazides in some patients. This has been attributed to the inhibition of renal prostaglandin synthesis. When treated concomitantly with NSAIDs, the patient should be closely monitored for signs of renal failure (See Section 4.4 Special warnings and precautions for use – Renal effects) and to ensure the efficacy of the diuretic.

It has been reported that the addition of triamterene to a maintenance regimen of indomethacin resulted in reversible renal failure in two of four healthy volunteers. ENDOL and triamterene should not be administered together.

Both indomethacin and potassium-sparing diuretics have been associated with increased plasma potassium levels. When these agents are administered concomitantly, the potential effects of ENDOL and potassium-sparing diuretics on potassium kinetics and renal function should be taken into consideration.

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

Cardiac Glycosides/Digoxin: It has been reported that indomethacin administered concomitantly with digoxin increases the serum concentration and prolongs the half-life of digoxin. Therefore, when ENDOL and digoxin are administered concomitantly, serum digoxin levels should be closely monitored.

Antihypertensive drugs: The concomitant administration of ENDOL with certain antihypertensive drugs may acutely attenuate their hypotensive effects, due in part to the inhibition of prostaglandin synthesis by indomethacin. Therefore, caution should be exercised when considering the addition of ENDOL 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, due to phenylpropanolamine given with ENDOL. The reason for this additive effect is partly the inhibition of prostaglandin synthesis by indomethacin. Caution should be exercised when ENDOL and phenylpropanolamine are administered concomitantly.

Corticosteroids: When administered with corticosteroids, the risk of gastrointestinal bleeding and ulceration associated with non-steroidal anti-inflammatory drugs is increased.

Mifepristone: Non-steroidal anti-inflammatory drugs and aspirin should be avoided for at least 8 to 12 days following the administration of mifepristone.

Quinolone antibiotics: It has been reported that 4-quinolones may cause convulsions in patients with or without a history of convulsions; the simultaneous intake of non-steroidal anti-inflammatory drugs may also cause convulsions.

4.6 Pregnancy and Lactation

General Advice

1st and 2nd Trimester Category: C

3rd Trimester Category: D

Women of childbearing potential/Birth control (Contraception)

No studies have been conducted on women of childbearing potential.

Pregnancy

Studies in animals are insufficient with respect to effects on pregnancy and/or embryonal/fetal development and/or parturition (birth) and/or postnatal development (see section 5.3). The potential risk for humans is unknown.

ENDOL should not be used during pregnancy unless necessary.

ENDOL should only be used during the first two trimesters of pregnancy if the potential benefit outweighs the potential risk to the fetus.

The known effects of indomethacin and other drugs in this class on the human foetus during the third trimester of pregnancy are as follows: prenatal constriction of the ductus arteriosus, tricuspid insufficiency, and pulmonary hypertension; failure of the ductus arteriosus to close after birth, which may be resistant to medical intervention; myocardial degenerative changes; platelet dysfunction resulting in bleeding; intracranial bleeding; renal dysfunction or renal failure; renal injury/dysgenesis which may result in prolonged or permanent renal failure; oligohydramnios; gastrointestinal bleeding or perforation; and an increased risk of necrotizing enterocolitis. The use of ENDOL is not recommended during the third trimester of pregnancy.

Lactation

The use of ENDOL is not recommended in breastfeeding mothers. Indomethacin passes into breast milk.

Reproductive ability / fertility

The effect on human fertility has not been reported.

4.7 Effects on driving and using machines

Patients should be warned that they may experience dizziness, light-headedness, visual disturbances, or headaches, and if they do, they should not drive or engage in activities that require alertness.

4.8 Undesirable effects

The following adverse effects are listed by system organ class and frequency. The frequency classification is as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very rare: Leukopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia, agranulocytosis, bone marrow depression, disseminated intravascular coagulation, and blood dyscrasias including, in particular, thrombocytopenia.

Rare: Angiitis.

Since anaemia may develop in some patients secondary to overt or occult gastrointestinal bleeding, appropriate blood tests are recommended.

Immune system disorders

Rare: Angioneurotic oedema, a sudden drop in blood pressure resembling a shock-like state, acute anaphylaxis.

Psychiatric disorders

Rare: Mental confusion, anxiety, syncope, light-headedness, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscle movements, insomnia, hallucinations, and depersonalisation, paraesthesia, dysarthria, worsening of epilepsy, and Parkinsonism.

These are usually transient and often disappear with continuation of treatment or dose reduction. However, in some cases, severe reactions require discontinuation of therapy.

Nervous system disorders

Not known: Headaches, dizziness, balance disorder, depression, vertigo, and fatigue (including malaise and apathy).

Eye disorders

Rare: Blurred vision, diplopia, and orbital and periorbital pain.

Corneal deposits and retinal disturbances, including of the macula, have been reported in patients with rheumatoid arthritis on long-term treatment; however, similar changes may be expected in rheumatoid arthritis patients not receiving indomethacin.

Ear and labyrinth disorders

Rare: Deafness.

Not known: Tinnitus, hearing problems.

Cardiovascular disorders

Rare: Oedema, increased blood pressure, tachycardia, chest pain, arrhythmia, palpitations, hypotension, congestive heart failure, increased blood urea, and haematuria.

Respiratory, thoracic and mediastinal disorders

Rare: Acute respiratory distress including sudden dyspnoea, asthma, and pulmonary oedema. Bronchospasm may be precipitated in patients with a current or past history of bronchial asthma or allergic disease.

Gastrointestinal disorders

Common: Nausea, anorexia, vomiting, epigastric distress, abdominal pain, constipation, and diarrhoea. Single or multiple ulcers may develop, including perforation and haemorrhage of the oesophagus, stomach, duodenum, or small or large intestine. Bleeding in the gastrointestinal tract without obvious ulcer formation, and increased abdominal pain when used in patients with ulcerative colitis.

Fatalities have been reported in some cases.

Rare: Stomatitis, gastritis, flatulence, bleeding from the sigmoid colon – either occult or from a diverticulum – and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma). Intestinal strictures (diaphragms) and intestinal ulceration followed by stenosis and obstruction.

Very rare: Tenesmus and irritation of the rectal mucosa (with suppositories).

Not known: Ulcerative colitis and regional ileitis.

Hepatobiliary disorders

Rare: Hepatitis and jaundice.

Some fatalities have been reported.

Skin and subcutaneous tissue disorders

Rare: Pruritus, urticaria, erythema nodosum, skin rash and photosensitivity, exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, hair loss.

Renal and urinary disorders

Rare: Proteinuria, nephrotic syndrome, interstitial nephritis, and renal failure.

General disorders and administration site conditions

Rare: Vaginal bleeding, hyperglycaemia, glycosuria, hyperkalaemia, hot flushes and sweating, epistaxis, breast enlargement including growth and tenderness, gynaecomastia, and ulcerative colitis.

Laboratory tests

Borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT) have been observed in less than 1% of patients treated 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 occur such as rash or eosinophilia, ENDOL should be discontinued.

False-negative results in the dexamethasone suppression test (DST) have been reported in patients being treated with ENDOL. Therefore, the results of this test should be interpreted with caution in these patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose and its treatment

The following symptoms may be observed after an overdose: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. Paraesthesia, numbness, and convulsions have also been reported.

Treatment is symptomatic and supportive. If the ingestion is recent, the stomach should be emptied as quickly as possible, and the correction of severe electrolyte abnormalities may 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. After the stomach has been emptied, 25 or 50 g of activated charcoal may be given. Depending on the patient's condition, close medical supervision and care may be necessary. The patient should be followed for several days, as gastrointestinal ulceration and haemorrhage have been reported as adverse reactions to indomethacin. The use of antacids may be helpful.
The plasma elimination of indomethacin is biphasic, with a terminal plasma half-life of between 2.6 and 11.2 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Acetic acid derivatives and related substances - Indomethacin
ATC code: M01AB01

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

5.2 Pharmacokinetic properties

General properties

Absorption

Indomethacin is administered orally, rectally, and parenterally. Following oral administration, indomethacin is rapidly and almost completely absorbed from the intestines, and peak plasma levels are reached in 0.5 to 2 hours. When taken with food, absorption is slowed but remains almost complete.

Distribution

It is approximately 90% bound to plasma proteins.

Biotransformation

It undergoes enterohepatic circulation. It is metabolised partly by O-demethylation and partly by N-deacetylation, and the unchanged drug and its metabolites are partially conjugated with glucuronic acid in humans.

Elimination

It is excreted both in urine and faeces unchanged and as its metabolites.

Linearity/Non-linear state

Relevant information is not available.

5.3 Preclinical safety data

Relevant information is not available.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Capsule content:

Lactose monohydrate

Starch

Colloidal silicon dioxide

Sodium lauryl sulfate

Magnesium stearate

Gelatin capsule:

Indigo carmine FD&C Blue 2 (E132)

Titanium dioxide (E171)

Gelatin

6.2 Incompatibilities

None.

6.3 Shelf Life

48 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of the packaging

Structure of the packaging material:

Blisters containing 25 capsules, consisting of one side made of transparent PVC foil and the other side of printed aluminum foil.

Each carton box contains 25 capsules.

6.6 Disposal of residual human medicinal products and other special precautions

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. MARKETING AUTHORIZATION HOLDER

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