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The MHRA granted Sandoz Limited Marketing Authorisations (licences) for the medicinal product Indometac 25mg and 50mg Capsules on 18th September 2007. These products, to be available by prescription only (POM), contain indometacin and are used to relieve pain, swelling and redness in a number of conditions affecting the joints and muscles, including rheumatism. They may also be used for other conditions, such as acute gout and period pain.

The active ingredient indometacin is part of a group of medicines called non-steroidal anti-inflammatory drugs, which cause a reduction in the levels of prostaglandins, substances believed to be responsible for causing pain and inflammation.

These applications are duplicates of previously granted applications for Indometacin 25mg and 50mg Capsules BP (PL 01274/0052-53), which were originally granted to Regent Laboratories Limited in 1979 and are currently owned by Regent-GM Laboratories Limited following a Change of Ownership that was granted in January 1995.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Indometacin 25mg and 50mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.
INDOMETACIN 25MG CAPSULES (PL 04416/0546)
INDOMETACIN 50MG CAPSULES (PL 04416/0547)

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Indometacin 25mg and 50mg Capsules (PL 04416/0546-7) to Sandoz Limited on 18th September 2007. The products are available as prescription-only medicines (POM).

The applications were submitted as simple abridged applications according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Indometacin 25mg and 50mg Capsules BP (PL 01274/0052-53), which were originally approved in 1979 to Regent Laboratories Limited and is currently owned by Regent-GM Laboratories Limited following a Change of Ownership that was granted in January 1995.

No new data were submitted nor were necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PAR was generated for these.

The active ingredient indometacin acts as a non-steroidal anti-inflammatory, reducing the levels of prostaglandins. Indometacin 25mg and 50mg Capsules are indicated for the treatment of:

1. Active stages of rheumatoid arthritis
2. Osteoarthritis
3. Ankylosing spondylitis.
4. Degenerative joint disease of the hip.
5. Acute musculoskeletal disorders.
7. Acute gout
8. Inflammation, pain and oedema following orthopaedic procedures.
9. Pain and associated symptoms of primary dysmenorrhoea
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 04416/0546-7
PROPRIETARY NAME: Indometacin 25mg and 50mg Capsules
ACTIVE(S): Indometacin
COMPANY NAME: Sandoz Limited
LEGAL STATUS: POM

1. INTRODUCTION

These are simple, piggy back applications for Indometacin 25mg and 50mg Capsules submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Sandoz Limited, Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.

The applications cross-refer to Indometacin 25mg and 50mg Capsules BP (PL 01274/0052-53), which were originally granted to Regent Laboratories Limited in 1979 and are currently owned by Regent-GM Laboratories Limited following a Change of Ownership that was granted in January 1995.

The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the products are Indometacin 25mg and 50mg Capsules. The products have been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain indometacin, equivalent to 25 or 50mg. They are to be stored in either (i) an aluminium/polyvinylchloride blister strip or (ii) a high density polyethylene container with a polypropylene cap or child-resistant cap. The pack sizes are 28, 42, 56, 84 and 112 capsules for the blister pack and 28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000 capsules for the polyethylene container. The applicant has stated that not all proposed packs are intended for marketing and that mock-ups of packaging will be submitted for approval before marketing any pack sizes.

The proposed shelf-life (24 months for the blister and 60 months for the container) and storage conditions (store in original packaging, keep container tightly closed) are consistent with the details registered for the cross-reference products.

2.3 Legal status

On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

Sandoz Limited, Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
With the exception of gelatin and lactose monohydrate, no materials of animal or human origin are included in these products. This is consistent with the cross reference product.

Lactose monohydrate is sourced from milk that is fit for human consumption and no animal materials, with the exception of bovine rennet, have been used in its manufacture. Satisfactory certificates of suitability have been provided for gelatin showing compliance with current guidelines concerning the minimising of BSE/TSE contamination.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summaries are consistent with the details registered for the cross-reference products.
6. **PATIENT INFORMATION LEAFLET/CARTON**

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

**Carton and blister**

The applicant has provided the proposed wording for the packaging and mock-ups for the 28 pack size of tablets. Confirmation has been provided that mock-ups of packaging for other proposed pack sizes will be provided before marketing of those packs takes place in the UK.

7. **CONCLUSIONS**

The data submitted with the applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

As these are duplicate applications, no new clinical data have been supplied and none are required.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to previously granted applications for Indometacin 25mg and 50mg Capsules BP (PL 01274/0052-53).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference product. Extensive clinical experience with indometacin is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.
INDOMETACIN 25MG CAPSULES (PL 04416/0546)
INDOMETACIN 50MG CAPSULES (PL 04416/0547)

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation applications on 16/04/2003.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 02/06/2003.</td>
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<td>Following assessment of the application the MHRA requested further information on 30/07/2003, 26/03/2004, 15/07/2004 and 06/01/2006.</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 27/02/2004, 16/04/2004, 10/06/2005 and 28/05/2007</td>
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<td>The applications were determined on 18/09/2007</td>
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INDOMETACIN 25MG CAPSULES (PL 04416/0546)
INDOMETACIN 50MG CAPSULES (PL 04416/0547)

STEPS TAKEN AFTER ASSESSMENT

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INDOMETACIN 25MG CAPSULES (PL 04416/0546)  
INDOMETACIN 50MG CAPSULES (PL 04416/0547)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Indometacin 25mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 25 mg of Indometacin.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
Indometacin capsules are presented as size 3, ivory opaque shells printed with 'IND 25' and logo

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Indometacin capsules are indicated for the following conditions.
1. Active stages of rheumatoid arthritis
2. Osteoarthritis
3. Ankylosing spondylitis.
4. Degenerative joint disease of the hip.
5. Acute musculoskeletal disorders.
7. Acute gout
8. Inflammation, pain and oedema following orthopaedic procedures.
9. Pain and associated symptoms of primary dysmenorrhoea

4.2 Posology and method of administration
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
For oral administration.

Chronic conditions
Adults: 25 mg two to four times daily increased if required, up to 200 mg daily.
The recommended oral dose range is 50 - 200 mg daily in divided doses.

Acute gouty arthritis:
Adults: 150 - 200 mg daily in divided doses until all signs and symptoms subside.

Dysmenorrhoea:
Up to 75 mg daily until the symptoms subside.
The capsules should preferably be administered with or after food, milk or antacid.

Pediatric dosage: Not established

Use in the 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.

4.3 Contraindications
1. Hypersensitivity to any of the constituents.
2. NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
3. Severe hepatic, renal and cardiac failure (see section 4.4 – Special warnings and precautions for use).
4. During the last trimester of pregnancy (See section 4.6 – pregnancy and Lactation).
5. Active or previous peptic ulcer.
6. History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
7. Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 – Interactions).
9. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

In all patients:
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).

Headache, dizziness and light-headedness can occur usually early in treatment. These disappear on continuing therapy or reducing the dosage but if headache persists despite dosage reduction, treatment should then be discontinued.

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

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.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependant 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 and the elderly. Renal function should be monitored in these patients (See also section 4.3 – Contraindications).

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.

Gastrointestinal bleeding without an obvious ulcer formation and perforation of pre-existing sigmoid lesions such as diverticulum and carcinoma can also occur.

Patients with a history of GI toxicity, particularly the 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).

Single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small or large intestine have been reported to occur rarely.

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

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 (See section 4.8 – Undesirable effects).
Gastrointestinal disturbances can be minimised by administering indometacin orally with food, milk, or an antacid. They usually disappear on reducing the dosage; if not, the risk of continuing therapy should be weighed against any possible benefits.

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).

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.

Caution should be exercised in patients with psychiatric disorders, epilepsy or Parkinsonism as indometacin may aggravate these conditions.

Indometacin may mask the signs and symptoms of infection therefore care should be taken in patients with existing, but controlled infection.

Eye changes can occur in patients suffering from rheumatoid arthritis, which may be related to the underlying disease or to the therapy. Ophthalmological examination at periodic intervals are recommended in these patients. Therapy should be discontinued in the event of changes in the eye. Patients should be screened periodically to detect early signs of adverse effects on peripheral blood, liver function or gastrointestinal tract.

Increase 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 hyporenaemic-hypoaldosteronism state.

4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (See section 4.3 – Contraindications).

Concurrent administration of diflunisal with indometacin increases plasma levels of indometacin by about a third with concomitant decrease in renal clearance. Fatal gastrointestinal haemorrhage can occur.

Anti-hypertensives: Reduced anti-hypertensive effect.

The 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).

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 prostaglandin synthesis. Caution should therefore be exercised when indometacin and phenylpropanolamine are administered concomitantly.

**Diuretics:** Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. In some patients, 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, patients should be observed to ascertain the diuretic effect.

Indometacin reduces basal plasma renin activity as well as those elevations of plasma renin activity induced by furosemide, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

Indometacin and triamterene should not be administered together as it may result in reversible acute renal failure.

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

**Lithium:** Decreased elimination of lithium.

Concurrent administration of indometacin and lithium produces elevation of plasma lithium and reduction in renal lithium clearance due to inhibition of prostaglandin synthesis, therefore during concomitant therapy patients should be carefully observed 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.

**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).

If the patient is receiving corticosteroids concomitantly with indometacin, a reduction in dosage in these may be possible but should only be effected slowly under supervision.

**Anti-coagulants:** 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 NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

**Tacrolimus:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Co-administration of probenecid may increase plasma levels of indometacin.

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 a discernable 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 risk to the foetus.

Indometacin crosses the placental barrier. Studies in humans have not been conducted. Studies carried out on rats and mice have shown that (at a dose of 4 mg/kg body weight/day) indometacin causes decreased average foetal weight and retarded ossification and when administered during the last three days of gestation there is increased evidence of neuronal necrosis in the diencephalon and some maternal and foetal deaths. Other studies in mice with higher doses (5 to 15 mg/kg body weight/day) have resulted in maternal toxicity and death, increased foetal resorption and congenital malformations.

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, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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, haematemeses, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, 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).

Cardiovascular: Oedema has been reported in association with NSAID treatment. More infrequently hypertension, chest pain, arrhythmia, tachycardia, palpitation, hypotension, congestive heart failure or rapid fall in blood pressure resembling a shock-like state.

Other adverse events reported less commonly include:
Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome, renal failure, hematuria and proteinuria.

Hepatic: abnormal liver function, hepatitis and jaundice.

Neurological and special senses: Visual disturbances, optic neuritis, orbital and periorbital pain, corneal deposits, retinal disturbances including those of the macula have been reported in patients with rheumatoid arthritis on long-term therapy, 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, drowsiness, anxiety, syncope, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscular movements, insomnia, dysarthria, aggravation of epilepsy and Parkinsonism.

**Haematological:** Thrombocytopenia, neutropenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia. Bone-marrow depression, disseminated intravascular coagulation, petechiae, ecchymosis and raised blood urea.

**Dermotological:** Photosensitivity.

Other reactions occurring infrequently are: angitis, alopecia, vaginal bleeding, hyperglycaemia, glycosuria, hyperkalaemia, flushing, sweating, epistaxis, breast changes, gynaecomastia and ulcerative stomatitis.

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).

**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.

### 4.9 Overdose

a) **Symptoms**

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

Numbness, paraesthesiae and convulsions have been reported.

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.

Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given.

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 because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indometacin. Use of antacids may be helpful.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patients clinical condition.

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

Indometacin inhibits the action of cyclo-oxygenase, hence decreases the formation of precursors of prostaglandins and thromboxanes from arachidonic acid.

The analgesic action of indometacin involves blocking pain impulse generation via a peripheral action that may result from inhibition of the synthesis of prostaglandins and possibly inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation. Inhibition of prostaglandin synthesis in the central nervous system may also contribute to the analgesic effect. Indometacin acts as anti-rheumatic via analgesic and anti-inflammatory mechanisms; the therapeutic effects are not due to pituitary-adrenal stimulation. The production of rheumatoid factor (IgM) may be decreased during indometacin therapy; however the medication does not affect the progressive course of rheumatoid arthritis.

Indometacin acts as an antigout agent via analgesic and anti-inflammatory mechanisms; it does not affect hyperuricaemia.

The exact mechanism for anti-inflammatory action has not been determined. It is thought to act peripherally in inflamed tissue, probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other local mediators of the inflammatory response. Inhibition of leucocyte migration, inhibition of the release and/or actions of lysosomal enzymes, inhibition of phosphodiesterase with resultant increase in intracellular cyclic adenosine monophosphate concentration and actions on other cellular and immunological processes in mesenchymal and connective tissue may be involved.

Indometacin has an antipyretic action. It produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased cutaneous blood flow, sweating and heat loss. The central action may involve inhibition of prostaglandin synthesis in the hypothalamus.

Indometacin also acts as an antidysmenorrheal by inhibiting the synthesis of uterine prostaglandin hence decreases uterine contractions, increases uterine perfusion and relieves ischaemic as well as spasmodic pain. Indometacin may also relieve extraterine symptoms resulting due to excessive prostaglandin production, such as headache, nausea and vomiting.

Other actions of indometacin includes reversible inhibition of platelet aggregation but to lesser extent than does aspirin.

Recovery of platelet function results within 1 day after discontinuation of the medication.

5.2 Pharmacokinetic properties

Following oral administration indometacin is absorbed rapidly and completely from the gastrointestinal tract. Approximately 90% of the dose is absorbed within 4 hours.

Absorption is slightly delayed when indometacin is administered concomitantly with food or an aluminium or magnesium containing antacid. Approximately 99% is bound to albumin.

Half-life is biphasic, distribution occurs in 1 hour and elimination in approximately 4.5 hours (usual range being 2.6 to 11.2 hours); and is subject to large interindividual variation, possibly due to interindividual differences in enterohepatic circulation and subsequent reabsorption. Onset of action as an antirheumatic usually occurs within 7 days but may require up to 14 days, depending on the severity of condition. Antigout action occurs within 2-4 hours. Peak plasma concentration is reached in 0.5-2.0 hours following an oral dose. Peak serum concentration for 25 mg and 50 mg capsule being 0.8-2.5 mcg/ml and 2.5-4.0 mcg/ml respectively.

Indometacin is metabolised in the liver, approximately 60% of a dose being excreted in urine (10-20% as unchanged indometacin) and 33% via the biliary route (1.5% as unchanged indometacin). It is also excreted in the breast milk.
5.3 **Preclinical safety data**
There are no other 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**

Talc  
Magnesium stearate  
Sodium starch glycollate  
Sodium lauryl sulphate  
Lactose monohydrate

Capsule shell components

Body:  
Quinoline yellow (E104)  
Erythrosine (E127)  
Titanium dioxide (E171)  
Gelatin

Cap:  
Quinoline yellow (E104)  
Erythrosine (E127)  
Titanium dioxide (E171)  
Gelatin

Printing Ink:  
Shellac glaze  
Iron oxide black (E172)  
Lecithin (Soya) (E322)  
Antifoam DC 1510 (Food grade)

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
5 years for opaque plastic containers.  
2 years for blister packaging.

6.4 **Special precautions for storage**
Plastic containers: Keep container tightly closed.  
Blister packs: Store in the original package.

6.5 **Nature and contents of container**

Indometacin capsules are packed in the following containers and closures.

- Opaque plastic containers composed of polypropylene tubes and polyethylene made tamper-evident closures. Pack sizes of 28, 42, 50, 56, 84, 100 capsules.

- Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child-resistant tamper-evident closure composed of high density polyethylene for all pack sizes (28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000) with a packing inclusion of standard polyether foam or polyethylene or polypropylene-made filler.

- Blister packs of aluminium opaque PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 42, 56, 84 and 112.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Not applicable.
MARKETING AUTHORISATION HOLDER
Sandoz Limited
Woolmer Way
Bordon
Hants
GU35 9QE

MARKETING AUTHORISATION NUMBER(S)
PL 04416/0546

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/09/2007

DATE OF REVISION OF THE TEXT
18/09/2007
1 NAME OF THE MEDICINAL PRODUCT
Indometacin 25mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 25 mg of Indometacin.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
Indometacin capsules are presented as size 3, ivory opaque shells printed with 'IND 25' and logo

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Indometacin capsules are indicated for the following conditions.
1. Active stages of rheumatoid arthritis
2. Osteoarthritis
3. Ankylosing spondylitis.
4. Degenerative joint disease of the hip.
5. Acute musculoskeletal disorders.
7. Acute gout
8. Inflammation, pain and oedema following orthopaedic procedures.
9. Pain and associated symptoms of primary dysmenorrhoea

4.2 Posology and method of administration
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
For oral administration.

Chronic conditions
Adults: 25 mg two to four times daily increased if required, up to 200 mg daily.
The recommended oral dose range is 50 - 200 mg daily in divided doses.

Acute gouty arthritis:
Adults: 150 - 200 mg daily in divided doses until all signs and symptoms subside.

Dysmenorrhoea:
Up to 75 mg daily until the symptoms subside.
The capsules should preferably be administered with or after food, milk or antacid.

Paediatric dosage: Not established

Use in the 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.

4.3 Contraindications
1. Hypersensitivity to any of the constituents.
2. NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
3. Severe hepatic, renal and cardiac failure (see section 4.4 – Special warnings and precautions for use).
4. During the last trimester of pregnancy (See section 4.6 – pregnancy and Lactation).
5. Active or previous peptic ulcer.
6. History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
7. Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 – Interactions).
9. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

In all patients:
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).

Headache, dizziness and light-headedness can occur usually early in treatment. These disappear on continuing therapy or reducing the dosage but if headache persists despite dosage reduction, treatment should then be discontinued.

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

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.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependant 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 and the elderly. Renal function should be monitored in these patients (See also section 4.3 – Contraindications).

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.

Gastrointestinal bleeding without an obvious ulcer formation and perforation of pre-existing sigmoid lesions such as diverticulum and carcinoma can also occur.

Patients with a history of GI toxicity, particularly the 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 gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (See section 4.5 – Interactions).

Single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small or large intestine have been reported to occur rarely.

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

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 (See section 4.8 – Undesirable effects).

Gastrointestinal disturbances can be minimised by administering indometacin orally with food, milk, or an antacid. They usually disappear on reducing the dosage; if not, the risk of continuing therapy should be weighed against any possible benefits.
**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).

**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.

Caution should be exercised in patients with psychiatric disorders, epilepsy or Parkinsonism as indometacin may aggravate these conditions.

Indometacin may mask the signs and symptoms of infection therefore care should be taken in patients with existing, but controlled infection.

Eye changes can occur in patients suffering from rheumatoid arthritis, which may be related to the underlying disease or to the therapy. Ophthalmological examination at periodic intervals are recommended in these patients. Therapy should be discontinued in the event of changes in the eye. Patients should be screened periodically to detect early signs of adverse effects on peripheral blood, liver function or gastrointestinal tract.

Increase in plasma potassium concentration including hyperkalaemia have been reported even in some patients without renal impairment.

In patients with normal renal function these effects have been attributed to a hyporeninaemic-hypoaldosteronism state.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Other analgesics:** Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (See section 4.3 – Contraindications).

Concurrent administration of diflunisal with indometacin increases plasma levels of indometacin by about a third with concomitant decrease in renal clearance. Fatal gastrointestinal haemorrhage can occur.

**Anti-hypertensives:** Reduced anti-hypertensive effect.

The 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).
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 prostaglandin synthesis. Caution should therefore be exercised when indometacin and phenylpropanolamine are administered concomitantly.

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

In some patients, 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, patients should be observed to ascertain the diuretic effect.

Indometacin reduces basal plasma renin activity as well as those elevations of plasma renin activity induced by furosemide, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

Indometacin and triameterene should not be administered together as it may result in reversible acute renal failure.

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

**Lithium:** Decreased elimination of lithium.

Concurrent administration of indometacin and lithium produces elevation of plasma lithium and reduction in renal lithium clearance due to inhibition of prostaglandin synthesis, therefore during concomitant therapy patients should be carefully observed 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.

**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).

If the patient is receiving corticosteroids concomitantly with indometacin, a reduction in dosage in these may be possible but should only be effected slowly under supervision.

**Anti-coagulants:** 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 NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

**Tacrolimus:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. Co-administration of probenecid may increase plasma levels of indometacin.
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 a discernable 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 risk to the foetus.

Indometacin crosses the placental barrier. Studies in humans have not been conducted. Studies carried out on rats and mice have shown that (at a dose of 4 mg/kg body weight /day) indometacin causes decreased average foetal weight and retarded ossification and when administered during the last three days of gestation there is increased evidence of neuronal necrosis in the diencephalon and some maternal and foetal deaths. Other studies in mice with higher doses (5 to 15 mg/kg body weight/ day) have resulted in maternal toxicity and death, increased foetal resorption and congenital malformations.

*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, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

**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, melena, 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.

**Hypersensitivity:** Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, 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).

**Cardiovascular:** Oedema has been reported in association with NSAID treatment. More infrequently hypertension , chest pain, arrhythmia, tachycardia, palpitation, hypotension, congestive heart failure or rapid fall in blood pressure resembling a shock-like state

Other adverse events reported less commonly include:

**Renal:** Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome, renal failure, hematuria and proteinuria.

**Hepatic:** abnormal liver function, hepatitis and jaundice.

**Neurological and special senses:** Visual disturbances, optic neuritis, orbital and peri-orbital pain, corneal deposits, retinal disturbances including those of the macula have been reported in patients with rheumatoid arthritis on long-term therapy, 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, drowsiness, anxiety, syncope, convulsions, coma, peripheral neuropathy,
muscle weakness, involuntary muscular movements, insomnia, dysarthria, aggravation of epilepsy and Parkinsonism.

**Haematological:** Thrombocytopenia, neutropenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia. Bone-marrow depression, disseminated intravascular coagulation, petechiae, ecchymosis and raised blood urea.

**Dermotological:** Photosensitivity.

Other reactions occurring infrequently are: angiitis, alopecia, vaginal bleeding, hyperglycaemia, glycosuria, hyperkalaemia, flushing, sweating, epistaxis, breast changes, gynaecomastia and ulcerative stomatitis.

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).

**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.

### 4.9 Overdose

**a) Symptoms**

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

Numbness, paraesthesiae and convulsions have been reported.

**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.

Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given.

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 because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indometacin. Use of antacids may be helpful.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patients clinical condition.

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

Indometacin inhibits the action of cyclo-oxygenase, hence decreases the formation of precursors of prostaglandins and thromboxanes from arachidonic acid.

The analgesic action of indometacin involves blocking pain impulse generation via a peripheral action that may result from inhibition of the synthesis of prostaglandins and possibly inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation. Inhibition of prostaglandin synthesis in the central nervous system may also contribute to the analgesic effect. Indometacin acts as anti-rheumatic via analgesic and anti-inflammatory mechanisms; the therapeutic effects are not due to pituitary-adrenal stimulation. The production of rheumatoid factor (IgM) may be decreased during indometacin therapy; however the medication does not affect the progressive course of rheumatoid arthritis.

Indometacin acts as an antigout agent via analgesic and anti-inflammatory mechanisms; it does not affect hyperuricaemia.

The exact mechanism for anti-inflammatory action has not been determined. It is thought to act peripherally in inflamed tissue, probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other local mediators of the inflammatory response. Inhibition of leucocyte migration, inhibition of the release and/or actions of lysosomal enzymes, inhibition of phosphodiesterase with resultant increase in intracellular cyclic adenosine monophosphate concentration and actions on other cellular and immunological processes in mesenchymal and connective tissue may be involved.

Indometacin has an antipyretic action. It produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased cutaneous blood flow, sweating and heat loss. The central action may involve inhibition of prostaglandin synthesis in the hypothalamus.

Indometacin also acts as an antidysemorrheal by inhibiting the synthesis of uterine prostaglandin hence decreases uterine contractions, increases uterine perfusion and relieves ischaemic as well as spasmodic pain. Indometacin may also relieve extrauterine symptoms resulting due to excessive prostaglandin production, such as headache, nausea and vomiting.

Other actions of indometacin includes reversible inhibition of platelet aggregation but to lesser extent than does aspirin.

Recovery of platelet function results within 1 day after discontinuation of the medication.

5.2 Pharmacokinetic properties

Following oral administration indometacin is absorbed rapidly and completely from the gastrointestinal tract. Approximately 90% of the dose is absorbed within 4 hours.

Absorption is slightly delayed when indometacin is administered concomitantly with food or an aluminium or magnesium containing antacid. Approximately 99% is bound to albumin.

Half-life is biphasic, distribution occurs in 1 hour and elimination in approximately 4.5 hours (usual range being 2.6 to 11.2 hours); and is subject to large interindividual variation, possibly due to interindividual differences in enterohepatic circulation and subsequent reabsorption. Onset of action as an antirheumatic usually occurs within 7 days but may require up to 14 days, depending on the severity of condition. Antigout action occurs within 2-4 hours. Peak plasma concentration is reached in 0.5-2.0 hours following an oral dose. Peak serum concentration for 25 mg and 50 mg capsule being 0.8-2.5 mcg/ml and 2.5-4.0 mcg/ml respectively.

Indometacin is metabolised in the liver, approximately 60% of a dose being excreted in urine (10-20% as unchanged indometacin) and 33% via the biliary route (1.5% as unchanged indometacin). It is also excreted in the breast milk.
5.3 Preclinical safety data
There are no other 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
Talc
Magnesium stearate
Sodium starch glycollate
Sodium lauryl sulphate
Lactose monohydrate

Capsule shell components

Body:
Quinoline yellow (E104)
Erythrosine (E127)
Titanium dioxide (E171)
Gelatin

Cap:
Quinoline yellow (E104)
Erythrosine (E127)
Titanium dioxide (E171)
Gelatin

Printing Ink:
Shellac glaze
Iron oxide black (E172)
Lecithin (Soya) (E322)
Antifoam DC 1510 (Food grade)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years for opaque plastic containers.
2 years for blister packaging.

6.4 Special precautions for storage
Plastic containers: Keep container tightly closed.
Blister packs: Store in the original package.

6.5 Nature and contents of container
Indometacin capsules are packed in the following containers and closures.
- Opaque plastic containers composed of polypropylene tubes and polyethylene made tamper-evident closures. Pack sizes of 28, 42, 50, 56, 84, 100 capsules.

- Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child-resistant tamper-evident closure composed of high density polyethylene for all pack sizes (28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000) with a packing inclusion of standard polyether foam or polyethylene or polypropylene-made filler.

- Blister packs of aluminium opaque PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 42, 56, 84 and 112.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable.
MARKETING AUTHORISATION HOLDER
Sandoz Limited
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MARKETING AUTHORISATION NUMBER(S)
PL 04416/0546

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
18/09/2007

DATE OF REVISION OF THE TEXT
18/09/2007
INDOMETACIN 25MG CAPSULES (PL 04416/0546)
INDOMETACIN 50MG CAPSULES (PL 04416/0547)

INDOMETACIN 25MG and 50MG capsules contain the active ingredient indometacin. Each capsule contains 25mg or 50mg of indometacin.

INDOMETACIN is a non-steroidal anti-inflammatory drug (NSAID) used to relieve pain, reduce inflammation, and treat a variety of conditions such as arthritis, dental procedures, pain after surgery, and menstrual cramps.

INDICATIONS AND USAGE
INDOMETACIN is indicated for the relief of pain associated with inflammatory, musculoskeletal, and/or peripheral vascular conditions, such as osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. It is also used for the relief of pain associated with dental procedures, surgery, and childbirth.

DOSAGE AND ADMINISTRATION
INDOMETACIN is taken orally. The usual adult dose is 25mg to 50mg, 3 to 4 times daily. The dose may be increased up to 100mg, 3 to 4 times daily, if needed. The maximum daily dose is 200mg.

SIDE EFFECTS
INDOMETACIN can cause side effects such as gastrointestinal discomfort, abdominal pain, nausea, and vomiting. Other possible side effects include dizziness, headache, rash, and increased risk of bleeding.

CONTRAINDICATIONS
INDOMETACIN is contraindicated in patients with a history of peptic ulcer disease, bleeding from peptic ulcers, or a history of hematemesis or melena.

WARNINGS
INDOMETACIN should be used with caution in patients with a history of hypertension, cardiac failure, or renal impairment.

PRECAUTIONS
INDOMETACIN should be used with caution in patients with a history of asthma, aspirin-sensitive asthma, or a history of urticaria or angioedema.

ADVERSE REACTIONS
INDOMETACIN can cause adverse reactions such as gastrointestinal bleeding, ulceration, and perforation. Other possible adverse reactions include agranulocytosis, aplastic anemia, and hemolytic anemia.

INTERACTIONS
INDOMETACIN can interact with other medications, including aspirin, warfarin, and oral anticoagulants. It can also interact with alcohol and other drugs that affect blood pressure.

DOSE AND ADMINISTRATION
INDOMETACIN 25mg Capsules
Each capsule contains 25mg of indometacin.

INDOMETACIN 50mg Capsules
Each capsule contains 50mg of indometacin.

INDICATIONS AND USAGE
INDOMETACIN is indicated for the relief of pain associated with inflammatory, musculoskeletal, and/or peripheral vascular conditions, such as osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. It is also used for the relief of pain associated with dental procedures, surgery, and childbirth.

DOSAGE AND ADMINISTRATION
INDOMETACIN is taken orally. The usual adult dose is 25mg to 50mg, 3 to 4 times daily. The dose may be increased up to 100mg, 3 to 4 times daily, if needed. The maximum daily dose is 200mg.

SIDE EFFECTS
INDOMETACIN can cause side effects such as gastrointestinal discomfort, abdominal pain, nausea, and vomiting. Other possible side effects include dizziness, headache, rash, and increased risk of bleeding.

CONTRAINDICATIONS
INDOMETACIN is contraindicated in patients with a history of peptic ulcer disease, bleeding from peptic ulcers, or a history of hematemesis or melena.

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INTERACTIONS
INDOMETACIN can interact with other medications, including aspirin, warfarin, and oral anticoagulants. It can also interact with alcohol and other drugs that affect blood pressure.

DOSE AND ADMINISTRATION
INDOMETACIN 25mg Capsules
Each capsule contains 25mg of indometacin.

INDOMETACIN 50mg Capsules
Each capsule contains 50mg of indometacin.

INDICATIONS AND USAGE
INDOMETACIN is indicated for the relief of pain associated with inflammatory, musculoskeletal, and/or peripheral vascular conditions, such as osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. It is also used for the relief of pain associated with dental procedures, surgery, and childbirth.

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INDOMETACIN is taken orally. The usual adult dose is 25mg to 50mg, 3 to 4 times daily. The dose may be increased up to 100mg, 3 to 4 times daily, if needed. The maximum daily dose is 200mg.

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CONTRAINDICATIONS
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WARNINGS
INDOMETACIN should be used with caution in patients with a history of hypertension, cardiac failure, or renal impairment.

PRECAUTIONS
INDOMETACIN should be used with caution in patients with a history of asthma, aspirin-sensitive asthma, or a history of urticaria or angioedema.

ADVERSE REACTIONS
INDOMETACIN can cause adverse reactions such as gastrointestinal bleeding, ulceration, and perforation. Other possible adverse reactions include agranulocytosis, aplastic anemia, and hemolytic anemia.

INTERACTIONS
INDOMETACIN can interact with other medications, including aspirin, warfarin, and oral anticoagulants. It can also interact with alcohol and other drugs that affect blood pressure.
Indometacin 50mg Capsules

Each capsule contains:
Indometacin 50mg

Other Ingredients include:
Lactose monohydrate

100 capsules

Sanoz Ltd., 37 Woolmer Way, Bordon, Hants, GU35 9OE

MHRA PAR – Indometacin 25mg and 50mg Capsules (PL 04416/0546-7) - 32 -
PATIENT INFORMATION LEAFLET
INDOMETACIN 25mg Capsules

Please read this leaflet carefully before you start taking your capsules. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

WHAT YOU SHOULD KNOW ABOUT THIS MEDICINE
Indometacin Capsules contain 25mg of indometacin as the active ingredient. They also contain the following other ingredients: talc, magnesium stearate, sodium starch glycolate, sodium lauryl sulphate, lactose monohydrate, quinoline yellow (E104), erythrosine (E127), titanium dioxide (E171), gelatin and printing ink (containing: shellac, iron oxide black (E172), soya lecithin (E322), antifoam DC 1510 (food grade)).

This medicine is available in pack sizes of 28, 42, 50, 56, 84, 100, 112, 250, 500 or 1000 capsules*.

The manufacturer of this medicine is: Regent-GM Laboratories Limited, 831 Coronation Road, Park Royal, London, NW10 7PT.

This medicine belongs to a group of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). These are used for pain relief and reducing inflammation.

This medicine is used to relieve pain, swelling and redness in a number of conditions affecting the joints and muscles including rheumatism. It may also be used for other conditions such as acute gout and period pain.

WHAT YOU SHOULD CHECK BEFORE TAKING THIS MEDICINE
Do not take this medicine if you are allergic to indometacin or any of the ingredients listed above.

Do not take this medicine if you are allergic to aspirin or other non-steroidal anti-inflammatory drugs e.g. ibuprofen, naproxen.

Do not take this medicine if you:
- have redness and soreness of the nasal cavity
- have, or have ever had, peptic ulceration (ulcer in your stomach or duodenum) or bleeding in your digestive tract
- have a history of repeated ulcers
- are taking any other non-steroidal anti-inflammatory drugs e.g. ibuprofen, naproxen.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Tell your doctor or pharmacist if you are taking any other medicines, including any that you can buy without a prescription. This is particularly important if you are taking:
- aspirin or other salicylates e.g. difunisal
- medicines to treat blood clotting e.g. warfarin
- diuretics (water tablets) such as furosemide and triamterene.
- medicines for high blood pressure such as ACE inhibitors (e.g. captopril or lisinopril), beta-blockers (e.g. propranolol or atenolol), hydralazine, losartan or alpha-blockers (e.g. doxazosin),
- probenecid (for gout)
- lithium (for mental illness)
- corticosteroids e.g. hydrocortisone cream (used in the treatment of infected skin disorders such as eczema and pruritis)
- ciclosporin (used in the treatment of graft rejection after transplantation)
- methotrexate (used in the treatment of acute leukaemias, tumours and rheumatoid arthritis)
- quinoline antibiotics e.g. ciprofloxacin or doxycycline.
- cardiac glycosides e.g. digoxin (used in the treatment of chronic heart failure)
- mifepristone (used for the termination of pregnancies [the "morning after pill"]).

Consult your doctor before taking this medicine if you suffer from mental illness, liver or kidney disease, heart disease, Parkinson’s disease, epilepsy, blood clot disorder, high blood levels of potassium, high blood pressure or a history of bronchial asthma, ulcerative colitis, or if you are pregnant or are breast feeding.

Indometacin may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems to become pregnant.

This medicine is not recommended during pregnancy or while breast feeding.

Consult your doctor if you are on antibiotic therapy i.e. if you have an infection.

If you are taking this medicine for a long time, eye examinations, liver and kidney function tests, abdominal tests and blood tests should be done periodically.

You could encounter headache, dizziness and light-headedness when you start taking this medicine. If it continues for a long period, stop taking the medicine and see your doctor immediately.

If you experience dizziness when you start taking this medicine, do not drive a car or do any activity requiring alertness.

Medicines such as indometacin may be associated with a small increased risk of heart attack (myocardial infarction) or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.
If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

**HOW TO TAKE THIS MEDICINE**
Swallow the capsules with water, milk or an antacid after a meal or snack as directed.

**DOSE:**
Adults: 50mg to 200mg per day in divided doses.

Elderly: Caution should be exercised and therapy should only start at the lowest recommended dose.

Children: Not recommended.

Your doctor will decide the dose that is best for you. The pharmacist's label will also tell you how many capsules to take and how often. If you are not sure about anything, ask your doctor or pharmacist.

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and continue with the regular dosing schedule. DO NOT DOUBLE THE DOSES.

If you think you have taken too many capsules, contact your doctor straight away or go to the nearest hospital casualty department. Take with you any remaining capsules and the container so that the medicine can be identified.

**AFTER TAKING THIS MEDICINE**

Along with the needed effects, this medicine may cause side effects in certain patients. The most common side effects are nausea, loss of appetite, vomiting, heartburn, abdominal pain, constipation, diarrhoea, headache, dizziness, light-headedness, depression, tiredness, feeling of illness and restlessness.

Rare side effects are mental confusion, hallucinations, anxiety, fainting, drowsiness, convulsions, coma, nervous system disorder, muscle weakness, speech problems, involuntary jerky movements, difficulty in sleeping, psychiatric problems, aggravation of epilepsy, shaking or stiffness, bleeding of the gastro-intestinal tract or oesophagus (this may be reduced by taking this medicine with an antacid), increased abdominal pain in patients with pre-existing ulcerative colitis, intestinal lesions followed by its narrowing and closure, stomach pain, mouth sores, gas, perforation of pre-existing lesions, swelling and lesions of the colon, inflammation (redness and swelling) of the ileum.

Reactions occurring infrequently are liver disease, yellowing of eyes and skin, swelling, high or low blood pressure, chest pain, fast or irregular heart beat, congestive heart failure, raised blood urea, blood in the urine, itching, hives, inflammation of arteries and veins, red painful nodules on the shins, thighs and forearms, skin rash, redness and scaling of the skin, a sensitivity of the skin to sunlight, Steven-Johnson syndrome, round red spots on the skin, decay and death of skin tissue, allergic reactions, breathing problems (may occur in patients with a history of asthma or allergic disease), blood disorder e.g. leucopenia, anaemia, thrombocytopenia, bone marrow depression and agranulocytosis (sore throat and fever), abnormal blood clotting, flat purplish-red spots on the skin, nailbed or mucous membranes, blurred or double vision, deposits in the eye, ringing in the ear, hearing disturbances, proteins and sugar in the urine, vaginal bleeding, high blood sugar, high blood levels of potassium, flushing, sweating, nose bleed, breast changes, excessive developments of breast in men and kidney disease.

Medicines such as indometacin may be associated with a small increased risk of heart attack (myocardial infarction) or stroke.

Consult your doctor if any of these symptoms persist or become troublesome.

If you suffer from any of the following at any time during your treatment STOP TAKING the medicine and seek immediate medical help:
- Pass blood in your faeces (stools/motions), pass black tarry stools, vomit any blood or dark particles that look like coffee grounds.

**STOP TAKING your medicine and tell your doctor if you experience:**
- Indigestion or heartburn, abdominal pain (pain in your stomach) or other abnormal stomach symptoms.

Tell your doctor or pharmacist if you notice any other unusual or unexpected symptoms.

This medicine may affect the results of some laboratory tests. Therefore it is important that you tell the doctor of hospital staff that you are taking indometacin if you need to have any tests carried out.

**STORING THIS MEDICINE**

Keep the container tightly closed.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

Unless your doctor tells you to, do not keep any capsules that you no longer need. Return them to the pharmacist.

Remember this medicine is for YOU. Do not give it to anyone else, even if their symptoms are the same as yours.

This medicine may harm them.

Do not take the capsules if the expiry date on the label has passed.

Date of revised leaflet: 02/2007 (to be amended after approval).

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PATIENT INFORMATION LEAFLET

INDOMETACIN 50mg Capsules

Please read this leaflet carefully before you start taking your capsules. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

WHAT YOU SHOULD KNOW ABOUT THIS MEDICINE

Indometacin Capsules contain 50mg of indometacin as the active ingredient. They also contain the following other ingredients: talc, magnesium stearate, sodium starch glycolate, sodium lauryl sulphate, lactose monohydrate, quinoline yellow (E104), erythrosine (E127), titanium dioxide (E171), gelatin and printing ink (containing: shellac, iron oxide black (E172), soya lecithin (E322), anti-floam DC 1510 (food grade)).

This medicine is available in pack sizes of 24, 42, 50, 56, 94, 100, 112, 250, 500 or 1000 capsules*.

The product licence holder of this medicine is: Sandoz Ltd, 37 Woolner Way, Bordon, Hampshire, GU35 9QE.

The manufacturer of this medicine is: Regent-GM Laboratories Limited, 861 Coronation Road, Park Royal, London, NW10 7PT.

This medicine belongs to a group of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). These are used for pain relief and reducing inflammation.

This medicine is used to relieve pain, swelling and redness in a number of conditions affecting the joints and muscles including rheumatism. It may also be used for other conditions such as acute gout and period pain.

WHAT YOU SHOULD CHECK BEFORE TAKING THIS MEDICINE

Do not take this medicine if you are allergic to indometacin or any of the ingredients listed above.

Do not take this medicine if you are allergic to aspirin or other non-steroidal anti-inflammatory drugs e.g. ibuprofen, naproxen.

Do not take this medicine if you:

• have redness and soreness of the nasal cavity
• have, or have ever had, peptic ulceration (ulcer in your stomach or duodenum) or bleeding in your digestive tract
• have a history of repeated ulcers
• are taking any other non-steroidal anti-inflammatory drugs e.g. ibuprofen, naproxen.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Tell your doctor or pharmacist if you are taking any other medicines, including any that you can buy without a prescription. This is particularly important if you are taking:

• aspirin or other salicylates e.g. diflunisal
• medicines to treat blood clotting e.g. warfarin
• diuretics (water tablets) such as furosemide and triamterene.
• medicines for high blood pressure such as ACE inhibitors (e.g. captopril or lisinopril), beta-blockers (e.g. propranolol or atenolol), hydralazine, losartan or alpha-blockers (e.g. doxazosin).
• probenecid (for gout)
• lithium (for mental illness)
• corticosteroids e.g. hydrocortisone cream (used in the treatment of infected skin disorders such as eczema and pruritus)
• ociclorpim (used in the treatment of graft rejection after transplantation)
• methotrexate (used in the treatment of acute leukaemias, tumours and rheumatoid arthritis)
• quinolone antibiotics e.g. ciprofloxacin or doxycycline.
• cardiac glycosides e.g. digoxin (used in the treatment of chronic heart failure)
• midazolam (used for the termination of pregnancies [the “morning after pill”]).

Consult your doctor before taking this medicine if you suffer from mental illness, liver or kidney disease, heart disease, Parkinson’s disease, epilepsy, blood clot disorder, high blood levels of potassium, high blood pressure or a history of bronchial asthma, ulcerative colitis, or if you are pregnant or are breast feeding.

Indometacin may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems to become pregnant.

This medicine is not recommended during pregnancy or while breast feeding.

Consult your doctor if you are on antibiotic therapy i.e. if you have an infection.

If you are taking this medicine for a long time, eye examinations, liver and kidney function tests, abdominal tests and blood tests should be done periodically.

You could encounter headache, dizziness and light-headedness when you start taking this medicine. If it continues for a long period, stop taking the medicine and see your doctor immediately.

If you experience dizziness when you start taking this medicine, do not drive a car or do any activity requiring alertness.

Medicines such as indometacin may be associated with a small increased risk of heart attack (myocardial infarction) or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.
If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

**HOW TO TAKE THIS MEDICINE**
Swallow the capsules with water, milk or an antacid after a meal or snack as directed.

**DOSE:**
**Adults:** 50mg to 200mg per day in divided doses.
**Elderly:** Caution should be exercised and therapy should only start at the lowest recommended dose.
**Children:** Not recommended.

Your doctor will decide the dose that is best for you. The pharmacist’s label will also tell you how many capsules to take and how often. If you are not sure about anything, ask your doctor or pharmacist.

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and continue with the regular dosing schedule. **DO NOT DOUBLE THE DOSES.**

If you think you have taken too many capsules, contact your doctor straight away or go to the nearest hospital casualty department. Take with you any remaining capsules and the container so that the medicine can be identified.

**AFTER TAKING THIS MEDICINE**
Along with the needed effects, this medicine may cause side effects in certain patients. The most common side effects are nausea, loss of appetite, vomiting, heartburn, abdominal pain, constipation, diarrhoea, headache, dizziness, light-headedness, depression, tiredness, feeling of illness and restlessness.

Rare side effects are mental confusion, hallucinations, anxiety, fainting, drowsiness, convulsions, coma, nervous system disorder, muscle weakness speech problems, involuntary jerky movements, difficulty in sleeping, psychiatric problems, aggravation of epilepsy, shaking or stiffness, bleeding of the gastro-intestinal tract or oesophagus (this may be reduced by taking this medicine with an antacid), increased abdominal pain in patients with pre-existing ulcerative colitis, intestinal lesions followed by its narrowing and closure, stomach pain, mouth sores, gas, perforation of pre-existing lesions, swelling and lesions of the colon, inflammation (redness and swelling) of the ileum.

Reactions occurring infrequently are liver disease, yellowing of eyes and skin, swelling, high or low blood pressure, chest pain, fast or irregular heart beat, congestive heart failure, raised blood uric acid, blood in the urine, itching, hives, inflammation of arteries and veins, red painful nodules on the skin, thighs and forearms, skin rash, redness and scaling of the skin, a sensitivity of the skin to sunlight, Steven-Johnson syndrome, round red spots on the skin, decay and death of skin tissue, loss of hair, a sudden fall in blood pressure, allergic reactions, breathing problems (may occur in patients with a history of asthma or allergic disease), blood disorder e.g. leucopenia, anaemia, thrombocytopenia, bone marrow depression and agranulocytosis (sore throat and fever), abnormal blood clotting, flat purplish-red spots on the skin, nailbed or mucous membranes, blurred or double vision, deposits in the eye, ringing in the ear, hearing disturbances, proteins and sugar in the urine, vaginal bleeding, high blood sugar, high blood levels of potassium, flushing, sweating, nose bleed, breast changes, excessive developments of breast in men and kidney disease.

Medicines such as indometacin may be associated with a small increased risk of heart attack (myocardial infarction) or stroke.

Consult your doctor if any of these symptoms persist or become troublesome.

If you suffer from any of the following at any time during your treatment STOP TAKING the medicine and seek immediate medical help:

- Pass blood in your faeces (stools/motions), pass black tarry stools, vomit any blood or dark particles that look like coffee grounds.

**STOP TAKING the medicine and tell your doctor if you experience:**

- Ingestion or heartburn, abdominal pain (pain in your stomach) or other abnormal stomach symptoms.

Tell your doctor or pharmacist if you notice any other unusual or unexpected symptoms.

This medicine may affect the results of some laboratory tests. Therefore it is important that you tell the doctor of hospital staff that you are taking indometacin if you need to have any tests carried out.

**STORING THIS MEDICINE**
Keep the container tightly closed.

**KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.**

Unless your doctor tells you to, do not keep any capsules that you no longer need. Return them to the pharmacist.

Remember this medicine is for YOU. Do not give it to anyone else, even if their symptoms are the same as yours. This medicine may harm them.

Do not take the capsules if the expiry date on the label has passed.

Date of revised leaflet: 09/2007 (to be amended after approval).

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MHRA PAR – Indometacin 25mg and 50mg Capsules (PL 04416/0546-7) - 36 -
INDOMETACIN 25MG CAPSULES (PL 04416/0546)
INDOMETACIN 50MG CAPSULES (PL 04416/0547)

LABELLING

For oral administration: Use as directed by your doctor.
Please read the enclosed leaflet before use in the original package.
Keep out of the reach and sight of children.
Indomethacin 25mg Capsules

Each capsule contains 25mg indomethacin.
Other ingredients include: Lactose monohydrate.

For oral administration:
Use as directed by your doctor.

Please read the enclosed leaflet. Store in the original package.

Keep out of the reach and sight of children.

PL 04416/0548
Sandoz Ltd,
Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.
Each capsule contains 50mg indometacin. Other ingredients include: Lactose monohydrate.

For oral administration: Use as directed by your doctor.

Please read the enclosed leaflet. Store in the original package.

Keep out of the reach and sight of children.

Sandoz Ltd, Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.