Brand Name : **INDOS-25 CAPSULE** **Generic Name** : Indometacin Capsules BP 25 mg		2021
Module 1 7	Administrative Information and Prescribing Information Product Information	**Confidential**

7 PRODUCT INFORMATION

a. Summary of Product Characteristics

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

INDOS-25 CAPSULE (Indometacin Capsules BP 25 mg)

2. Qualitative and Quantitative Composition:

Qualitative Composition

Each capsule contains:
Indometacin BP 25 mg

Quantitative Composition

Ingredients	Specification	Label Claim	Qty. / Cap
ACTIVE			
Indometacin	BP	25 mg	26.250 mg
NON ACTIVE			
Maize starch	BP	-	126.25 mg
Purified talc	BP	-	23.750 mg
Colloidal anhydrous silica	BP	-	2.000 mg
Empty hard gelatin capsules Size: 3 Ivory/Ivory printed/ Indo-25 Alternately	Inhouse	-	1 Capsule

3. Pharmaceutical form:

Ivory/Ivory coloured hard gelatin capsules of size “3” having printed “INDO” and “25” on cap and body alternatively containing white powder.

4. Clinical particulars:

4.1 Therapeutic Indications:

Rheumatoid arthritis

Indomethacin has been used very extensively for over 20 years and has the reputation for being the most effective, through perhaps not the best tolerated, NSAID. Patients with R A frequently start on less potent agents and move towards indomethacin when pain control is found to be inadequate. Those patients with the more severe from of rheumatoid arthritis require careful assessment to determine the mechanism. If there is evidence that the disease is active, based on clinical signs(swollen, warm, tender joints) and biochemical and other tests (raised ESR, high-acute-phase proteins, low serum albumin), then one of the suppressant drugs such as gold or penicillamine is usually required and should be given under careful supervision. These act in the long term. Indomethacin is usually effective in about an hour and, in the case of the slow-release preparation, may last for 12-24 h. This produces symptomatic relief in the short term. The patient needs to understand the difference between the two types of drug.

The efficacy of indomethacin is not doubted and the literature summarized by Rhymer and Gengos is large. Most studies suggest that indomethacin is more effective than aspirin and clinical experience suggests that it is more powerful than most other NSAIDs. Unfortunately, comparative studies are difficult since patients with R A show considerable intra- and intersubject variability.

Osteoarthritis

All non-steroidal anti-inflammatory drugs may be expected to reduce the pain and discomfort experienced by patients with osteoarthritis. Normally patients respond satisfactorily to one of the less potent, better tolerated, NSAIDs and therefore one of these is used first. Indomethacin is usually reserved for those patients in whom less potent drugs, weight loss, and physiotherapy have not proved successful and surgery is inappropriate.

Ankylosing spondylitis

Idomethacin would now be considered by many to be the first choice for patients with painful ankylosing spondylitis.

Gout

NSAIDs are used to control the acute pain and inflammation in an acute attack of gout. They have little or no place in prophylaxis. Since the pain of gout is severe, one of the more potent NSAIDs tend to be used to control it. In this situation indomethacin, given as short-acting capsules, is a drug of first choice.

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Dysmenorrhea

There are many different drugs used to treat this problem. If a drug with prostaglandin-inhibiting properties is felt desirable to treat a particular patient, one of the better tolerated propionic acid derivatives would be preferable in the first instance.

Other non-specific musculoskeletal pain

Pain caused by incompletely diagnosed disorders affecting joints, tendons, muscles, or ligaments may respond to an NSAIDs. One of the less potent propionic acid derivatives is usually used and would be considered preferable to indomethacin. However more severe acute pains such as pleurisy may respond well to indomethacin.

Pain in malignant disease

Pain is frequently an important symptom in patients suffering from malignant disease, particularly when the disease has spread. There are many potential causes ranging from pressure on a nerve to constipation. Patients with metastases in bones or in other tissues develop an inflammatory response in which prostaglandins are involved. In this situation indomethacin may effectively reduce pain.

4.2 Posology and Method of Administration:

The usual initial dose by mouth in chronic musculoskeletal and joint disorders is 25 mg two or three times daily with food, increased, if required by 25 to 50 mg daily at weekly intervals to 150 to 200 mg daily. To alleviate night pain and morning stiffiness, 100 mg may be administered by mouth, or rectally as a suppository, on retiring. The total daily combined dose by mouth and by rectum should not exceed 200 mg. In acute gouty arthritis a suggested dose is 50 mg three times daily initially with rapidly reducing doses but up to 200 mg daily may be required; in dysmenorrhoea up to 75 mg daily has been suggested.

Method of administration : Oral.

4.3 Contraindications:

Upper gastrointestinal tract bleeding

Any patient who is at risk of suffering from upper gastrointestinal tract bleeding should not be given indomethacin. Indigestion may be considered a relative contraindication whereas patients with active pepticulceration should not be given indomethacin.

Indomethacin can be used in anticoagulated patients, but close monitoring is essential. Suggestions for trying to cope with this problem are given in mode of use (above)

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Fluid retention

Indomethacin and other NSAIDs cause fluid retention, probably by an effect on the kidneys involving prostaglandins. In some patients this causes general feelings of malaise and headaches, but in patients with heart failure the administration of indomethacin may provoke a significant deterioration. Similarly, patients with hypertension are more difficult to control if they are given drugs which cause fluid retention.

Allergy

Patients with nasal polyps or history of sensitivity to aspirin or similar drugs should not be given indomethacin.

4.4 Special Warnings and Precautions for Use :

Indometacin should not be given to patients with peptic ulcer or a history of gastrointestinal lesions or those who have experienced hypersensitivity reactions with aspirin or other NSAIDS. It should be administered with caution to patients with impaired renal or hepatic functions and to those with bleeding disorders, epilepsy, parkinsonism, psychiatric disorders. Indometacin may mask the signs and symptoms of infection and should be used with caution in patients with existing infection. Indometacin should be used with caution in patients with cardiac dysfunction, hypertension, and other condition associated with fluid retention.

Indometacin should not be given to neonates with untreated infection, with significantly impaired renal function or with necrotising enterocolitis. Infants who are bleeding (gastrointestinal bleeding, intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should not be given Indometacin.

4.5 Interaction with other medicinal products, and other forms of interaction:

Potentially hazardous interactions

Anticoagulants

Indomethacin may occasionally cause ulceration of the upper gastrointestinal tract. This may be associated with bleeding which could be severe if the patient is anticoagulated.

Alcohol and smoking

Smoking and alcohol may predispose to gastric and duodenal ulceration and excessive indulgence should be avoided by patients on indomethacin.

Lithium

Indomethacin and a number of other NSAIDs inhibit lithium excretion and may thereby produce by higher blood levels and toxicity. Patients taking lithium who require an NSAID should under go more careful monitoring of plasma lithium concentrations.

Triamterene

Indomethacin and triamterene should not be given together; the addition of triamterene to maintenance doses of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers.

Other significant interactions

Diuretics

Indomethacin causes fluid retention probably by an action on prostaglandins in the kidney. In this way indomethacin tends to counteract the effects of diuretics.

Antihypertensive drugs

Indomethacin probably opposes the effects of all antihypertensive drugs by the fluid-retaining actions noted above.

Diflunisal

This drug should not be given together with indomethacin

Sulfonylureas

Although indomethacin has not been shown to interact seriously with sulfonylureas, the prescriber should note that some NSAIDs do inhibit the metabolism of sulfonylureas and displace diabetic from protein binding sites. Increased care over diabetic control would seem prudent if patients on a sulfonylurea are put on any NSAID.

Potentially useful interactions

None has been reported.

4.6 Pregnancy and Lactation:

Prostaglandins are involved in the closure of the ductus arteriosus. Indomethacin should therefore never be given to women in the last trimester of pregnancy and it would seem sensible not to give indomethacin in pregnancy at all.

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4.7 Effects on ability to drive and use machines:

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Indometacin Capsules should refrain from driving or using machines.

4.8 Undesirable effects:

Potentially life-threatening effects

Deaths caused directly by indomethacin are rare. Serious gastrointestinal hemorrhage, particularly in individuals aged over 60 years, is a serious risk. In this age group, 1 in 1000 have a peptic ulcer bleed each year and 35 %of these are attributable to non aspirin NSAID use. Different NSAIDs increase the risk of bleeding by variable amount, which have been expressed as odds ratios from 2 to 31.5. Indomethacin has an odds ratio of 11.3. Hyperkalemia, marrow suppression causing leucopenia and thrombocytopenia, and the Stevens-Johnson syndrome are less common. Hepatitis is rare.

Symptomatic adverse effects

Symptomatic adverse effects are relatively common and usually affect the gastrointestinal tract, the CNS or the patient's fluid and electrolyte status. Upper abdominal discomfort, nausea, and anorexia occur in up to 10 %of patients; lower abdominal pain and bowel disturbances are less common. The most common adverse effects on the CNS are headache, dizziness, and tinnitus; somnolence, fatigue, and confusion are less common.

Some degree of fluid retention probably occurs in most patients. It causes non-specific bloating and general malaise in some, and occasionally precipitates overt signs of heart failure in susceptible patients.

All the above symptoms would be expected to resolve rapidly when the drug is withdrawn.

Other effects

Hyperglycemia and hyperkalemia may occur. Borderline elevations of one of more liver tests may be observed and significant elevation of alanine aminotransferase (serum glutaminic pyruvic transaminase) or aspartate aminotransferase (serum glutamic oxaloacetic transaminase) 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, the drug should be stopped.

4.9 Overdose:

Overdosage with indomethacin may cause by following symptoms: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation or lethargy. There have been reports of paresthesiae, numbness, and convulsions. Some gastrointestinal bleeding would be expected.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Indomethacin is effective in relieving pain and reducing the temperature in febrile patients. It is also a useful anti-inflammatory drug in the treatment of inflammatory disorders. Thus in rheumatoid arthritis it relives pain and reduces joint swelling but rarely affects the ESR or other measures of disease activity. It has no effect on the progression of the disease process. Indomethacin has actions on the platelet because the drug prevents the formation of thromboxane A by the platelet. The platelets are thus rendered less sticky. Indomethacin by inhibiting prostaglandin synthesis in the uterus, prolongs gestation by delaying the onset of labor. Prostaglandins of the E and F series are potent uterotropic agents and their biosynthesis is normally increased in the hours before parturition.

Indomethacin has little effect on renal function in normal individuals but can precipitate renal failure in patients who depend upon the vasodilatory action of prostaglandin E to maintain renal blood flow. This occurs in hypertension, diabetes, cirrhosis of the liver, and a number of other conditions. Indomethacin may cause hyperkalemia by suppressing the prostaglandin-induced secretion of rennin and this action may be useful in the treatment of Bartter's syndrome. Indomethacin also promotes salt and water retention by interfering with the prostaglandin induced inhibition of both chloride reabsorption and the action of ADH. Prostaglandins, particularly PGI_2 and PGE_2, are synthesized by the gastric mucosa and seem to promote the secretion of cytoprotective mucus. Indomethacin by inhibiting the synthesis of these prostaglandins, may lead to gastric erosions and ulceration. Prostaglandins have been implicated in keeping the ductus arteriosus patent after birth, and indomethacin is therefore used to close the ductus arteriosus as an alternative to surgical treatment.

5.2 Pharmacokinetic Properties:

There are several assay methods for indomethacin, many in journals which are not readily accessible. The gas chromatographic method of Evans using an electron capture detector would seem to be most sensitive, with a limit of detection of 10 $mg.1^{-1}$

Following oral administration indomethacin is rapidly and almost completely absorbed although occasionally absorption may be considerably delayed so that peak plasma concentrations may be obtained 30-120 min postdosing. There is considerable

interand intrasubject variation in the plasma concentration-time curves. Food delays absorption, but does not reduce overall bioavailability.

Rectal administration produces earlier but lower peak plasma concentrations. The overall bioavailability after rectal indomethacin is 80%.

Intra- and intersubject variability has been observed and half lives of 1-16 h have been recorded though 3-4.5 h is the range normally quoted. An unpredictable amount of enterohepatic recycling may contribute to the variability.

Indomethacin is 90-94% protein bound and has a volume of distribution of 0.34-1.571 kg. Only very small amounts pass into the brain, and into breast milk; some crosses the placenta. Penetration into the synovial fluid is slow, peak concentrations occurring about 1h after and comprising about 25% of peak plasma concentrations.

Pharmacokinetic data are surprisingly variable. Two reports on indomethacin contains wide ranges for each of major pharmacokinetic parameters. Examples include75-99% for protein binding and 30-300 min for time to peak after oral administration.

The limited number of pharmacokinetic studies in the elderly suggest that pharmacoconcentrations are comparable to young and older adults. In the neonate, there is a surprising amount of information on drug handling since indomethacin has been used to treat premature infants with a patent ductus arteriosus. Although protein binding is similar in the neonate to that in the adult, absorption and bioavailability are reduced. Pharmacokinetic studies on patients with rheumatoid arthritis reveal results comparable to those found in normal volunteers, a surprising observation since protein binding to albumin might be expected to be influenced by the protein changes in inflammatory disease. Plasma concentration curves are not significantly altered in renal disease but there are relatively few data on patients with liver disease.

Oral absorption	100%
Presystemic metabolism	low
Plasma half-life	
range	1-16h
mean	4 h
Volume of distribution	1 $I.kg^{-1}$
Plasma protein binding	90-99%

Indomethacin is extensively metabolized in the liver. The major route of elimination is in the urine; about 60% of the dose in 48 h, 5-20% of which is unchanged indomethacin, the pH of the urine affecting the amount. Only a small amount is excreted unchanged in the feces.

Concentration-effect relationship

There is no clear relationship between the plasma concentration if indomethacin and its therapeutic effect. There is, however, a direct negative relationship between the plasma concentration of the drug and prostaglandin levels in humans.

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Metabolism

The major route of elimination is by biotransformation in the liver and involves glucuronidation, O-demethylation, and N-deacylation. The major metabolites are desmethyl indomethacin (DMI), deschlorobenzoyl indomethacin (DBI), and desmethyldeschlorobenzoyl indomethacin (DMBI) and their glucuronides. In 48 h, 5-20% of the dose is excreted as unchanged drug in the urine, 6-26% as its glucuronide, 8-23% DBI and its glucuronide 4-20% as DBI and its glucuronide and <3% as DMBI and its glucuronide. Up to 16% of the dose is excreted in the feces as DMBI and up to 12% as DMI, with very small amounts of free indomethacin and DBI.

5.3 Pre-clinical safety data:

Subacute and chronic toxicity testing in a variety of laboratory animals have revealed that gastrointestinal ulceration is the major toxic effect. Teratogenicity and carcinogenicity tests have not revealed any significant positive effects. Very large doseshave adversely affected mother and fetus, led to resorption of the fetus and delayed parturition.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Maize starch	BP
Purified talc	BP
Colloidal anhydrous silica	BP
Empty hard gelatin capsules Size: 3 Ivory/Ivory printed/ Indo-25 Alternately	Inhouse

6.2 Incompatibilities:

None reported.

6.3 Shelf-Life:

36 months from the date of manufacture.

6.4 Special Precautions for Storage:

Store in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:

1. 10 capsules packed in one blister. Such 10 blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

2. Jar Pack of 1000 capsules.

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6.6 Special precautions for disposal:
None reported.

7. Registrant:
AGOG PHARMA LTD.
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9. Date of revision of the text :