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This information is intended for use by health professionals

1. Name of the medicinal product

INDOMETHACIN CAPSULES BP 25mg

2. Qualitative and quantitative composition

Each capsule contains 25mg Indomethacin Ph Eur.

3. Pharmaceutical form

Ivory hard gelatin capsules with Printing “INDO 25”

4. Clinical particulars

4.1 Therapeutic indications

Indomethacin has non-steroidal analgesic and anti-inflammatory properties.

It is indicated for the following conditions:

• active stages of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, degenerative joint disease of the hip, acute musculoskeletal disorders, gout and lumbago.

• inflammation, pain and oedema following orthopaedic procedures.

• treatment of pain and associated symptoms of primary dysmenorrhoea.

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

4.2 Posology and method of administration

Posology

The dosage should be carefully adjusted according to the needs of the individual patient.

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

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

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

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

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

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

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

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

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

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

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children: Safety for use in children has not been established.

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

Method of Administration

For oral administration.

To be taken preferably with or after food.

4.3 Contraindications

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

• Hypersensitivity to Indomethacin or to any of the excipients.

• Severe heart failure, hepatic failure and renal failure (see section 4.4).

• Not to be used in patients who have nasal polyps

• During the last trimester of pregnancy (see section 4.6).

• Safety in children has not been established.

• Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

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

4.4 Special warnings and precautions for use

• 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).

• The use of Indomethacin capsules with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided (see section 4.5)

• *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 Indomethacin.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Indomethacin 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).

• Indomethacin should be used cautiously in patients with impaired renal function, bleeding disorders, psychiatric disorders, epilepsy or parkinsonism, as it may tend to aggravate these.

• Gastro-intestinal disturbances may be minimised by giving Indomethacin orally with food, milk or an antacid. They usually disappear on reducing the dosage; if not, the risks of continuing therapy should be weighed against the possible benefits.

• Indomethacin may mask the signs and symptoms of infection, so antibiotic therapy should be initiated promptly if an infection occurs during therapy with Indomethacin. It should be used cautiously in patients with existing but controlled infection. Caution is advised with concomitant use of live vaccines.

• During prolonged therapy, periodic ophthalmic examinations are recommended, as corneal deposits and retinal disturbances have been reported. In patients with rheumatoid arthritis, eye changes may occur which may be related to the underlying disease or to the therapy.

Therefore, in chronic rheumatoid disease, ophthalmological examinations are periodic intervals are recommended. Therapy should be discontinued if eye changes are observed.

• Patients should be carefully observed to detect any unusual manifestations of drug sensitivity.

• *Cardiovascular, Renal and Hepatic Impairment:*

In patients with renal, cardiac, hepatic impairment, hypertension, heart failure or conditions predisposing to fluid retention caution is required since the use of NSAIDs may result in deterioration of renal function (see section 4.8). The dose should be kept as low as possible and renal function should be monitored. NSAIDs may also cause fluid retention which may further aggravate these conditions.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a NSAID may precipitate overt renal decompensation. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, the elderly, diabetes mellitus, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. Indomethacin should be given with caution and renal function should be monitored in these patients (see also section 4.3).

Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

• *Elderly:*

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

• *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.

• Caution is advised in patients with pre-existing sigmoid lesions (such as diverticulum or carcinoma) (or the development of these conditions) as

Indomethacin can aggravate these conditions.

• *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 previous history of serious GI events.

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

The risk of GI bleeding, ulceration or perforation is higher with increasing

NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

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).

• *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).

• *Impaired female fertility:*

The use of Indomethacin 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 Indomethacin should be considered.

• Indomethacin should be used with caution in patients with coagulation defects as Indomethacin can inhibit platelet aggregation. This effect may be exaggerated in patients with underlying haemostatic defects. Inhibition of platelet aggregation usually disappears within 24 hours of discontinuing Indomethacin.

• Caution is required in post-operative patients as bleeding time is prolonged (but within normal range) in normal adults.

• During prolonged therapy, periodic ophthalmic examinations are recommended, as corneal deposits and retinal disturbances have been reported. In patients with rheumatoid arthritis, eye changes may occur which may be related to the underlying disease or to the therapy.

Therefore, in chronic rheumatoid disease, ophthalmological examinations are periodic intervals are recommended. Therapy should be discontinued if eye changes are observed.

• Patients should be periodically observed to allow early detection of any unwanted effects on peripheral blood (anaemia), liver function (see section 4.8), or gastrointestinal tract especially during prolonged therapy.

• Medication Overuse Headache (MOH):

After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with medication overuse headache should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

• Avoid concomitant use of two or more NSAIDs.

• *Dermatological:*

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Indomethacin capsules should be discontinued at the first appearance of skin rash, mucosal lesions, and any other sign of hypersensitivity.

• Increases in plasma potassium concentration, including hyperkalaemia have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninaemic-hypoaldosteronism state.

4.5 Interaction with other medicinal products and other forms of interaction

• *Other analgesics including cyclooxygenase-2 selective inhibitors:* Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

• Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

• Antidiabetics: the effect of sulphonylureas may be increased by NSAIDs.

• Antihypertensives: Reduced anti-hypertensive effect. Indomethacin may acutely reduce the antihypertensive effect of beta-blockers due partly to Indomethacin's inhibition of prostaglandin synthesis. Patients receiving dual therapy should have the antihypertensive effect of their therapy reassessed. Therefore, caution should be exercised when considering the addition of Indomethacin to the regimen of a patient taking any of the following antihypertensive agents: alpha-adrenergic blocking agents, ACE inhibitors, beta-adrenergic blocking agents, angiotensin-2-receptor antagonists, hydralazine or nifedipine. An increased risk of hyperkalaemia has also been reported when NSAIDs are taken with ACE inhibitors.

• Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

• Antipsychotics: increased drowsiness with Indomethacin and haloperidol.

• Antivirals: Risk of Indomethacin toxicity with ritonavir, avoid concomitant use.

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

• Ciclosporin: Increased risk of nephrotoxicity. Administration of NSAIDs concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking ciclosporin, and renal function should be monitored carefully.

• Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

• Cytotoxics: Indomethacin may decrease the tubular secretion of methotrexate thus potentiating toxicity; simultaneous use should be undertaken with caution.

• Desmopressin: effect potentiated by Indomethacin.

• Diflunisal: avoid concomitant use. Increased plasma levels of Indomethacin by about a third with a concomitant decrease in renal clearance. Fatal gastro-intestinal haemorrhage has occurred.

• Diuretics: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Indomethacin may reduce the diuretic and antihypertensive effect of thiazides and furosemide in some patients. Indomethacin may cause blocking of the furosemide -induced increase in plasma renin activity. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

• Lithium: Decreased elimination of lithium.

Indomethacin is an inhibitor of prostaglandin synthesis and therefore the following drug interactions may occur; Indomethacin may raise plasma lithium levels and reduce lithium clearance in subjects with steady state plasma lithium concentrations. At the onset of such combined therapy, plasma lithium concentration should be monitored more frequently.

• *Methotrexate:* Decreased elimination of methotrexate.

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

• Muscle Relaxants: increased risk of baclofen toxicity due to reduced rate of excretion.

• Pentoxifylline: possible increased risk of bleeding when taken with NSAIDs.

• Probenecid: co-administration of probenecid may increase Indomethacin plasma levels. When increases in the dose of Indomethacin are made under these circumstances, they should be made cautiously and in small increments.

• *Quinolone antibiotics:* Animal data indicate the NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

• Salicylates: use of Indomethacin with aspirin or other salicylates is not recommended because there is no enhancement of therapeutic effect while the incidence of gastro-intestinal side-effects is increased. Moreover, co-administration of aspirin may decrease the blood concentration of Indomethacin.

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

• Tiludronic acid: the bioavailability of tiludronic acid is increased by Indomethacin.

• Triamterene: **Indomethacin** and triamterene should not be administered together since reversible renal failure may be induced.

• *Zidovudine:* Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

• Laboratory tests: false-negative results in the dexamethasone suppression test (DST) in patients being treated with Indomethacin have been reported. Thus, results of this test should be used with caution in these patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Indomethacin should not be given unless clearly necessary. If Indomethacin is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy to:

- possible prolongation of bleeding time, an anti-aggregating effect, which may occur even at very low doses

- inhibition of uterine contractions resulting in delayed or prolonged labour

Consequently Indomethacin is contraindicated during the third trimester of pregnancy.

Lactation:

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

• *Blood and lymphatic disorders:* blood dyscrasias (such as thrombocytopenia,

neutropenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia), bone marrow depression, petechiae, ecchymoses, purpura, and disseminated intravascular coagulation may occur infrequently. As some patients manifest anaemia secondary to obvious or occult gastro-intestinal bleeding, appropriate blood determinations are recommended. Epistaxis has been reported rarely.

• *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, rhinitis or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

• *Metabolic and nutrition disorders:* Hyperglycaemia, glycosuria, hyperkalaemia has been reported rarely.

• *Nervous system disorders:* Visual disturbances, optic neuritis, tinnitus, headache, dizziness and lightheadedness are common side effects**.** Starting therapy with a low dose and increasing gradually minimises the incidence of headache. These symptoms frequently disappear on continued therapy or reducing the dosage, but if headache persists despite dosage reduction, Indomethacin should be withdrawn. Other CNS effects include reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus or mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, vertigo, fatigue, malaise, dysarthria, syncope, coma, cerebral oedema, nervousness**,** confusion, anxiety and other psychiatric disturbances, depersonalisation, hallucinations**,** drowsiness, convulsions and aggravation of epilepsy and parkinsonism, peripheral neuropathy, paraesthesia, involuntary movements and insomnia. These effects are often transient and abate or disappear on reduced or stopping treatment. However, the severity of these may, on occasion, require cessation of therapy**.**

• *Eye disorders:* blurred vision, diplopia, optic neuritis and orbital and peri-orbital pain are seen infrequently. Corneal deposits and retinal or macular disturbances have been reported in some patients with rheumatoid arthritis on prolonged therapy with Indomethacin. Ophthalmic examinations are desirable in patients given prolonged treatment.

• *Ear and labyrinth disorders:* tinnitus or hearing disturbances (rarely deafness) have been reported.

• *Cardiac disorders:* There have been reports of hypotension, tachycardia, chest pain, arrhythmia, palpitations.

• *Cardiovascular and cerebrovascular:*

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

• *Vascular disorders:* flushing has been reported rarely.

• *Respiratory, thoracic and mediastinal disorders*: pulmonary eosinophilia. There may be bronchospasm in patients with a history of bronchial asthma or other allergic disease.

• *Gastrointestinal disorders:* The most commonly-observed adverse events are gastrointestinal in nature. Anorexia, epigastric discomfort,ulceration at any point in the gastro-intestinal tract (even with resultant stenosis and obstruction), bleeding (even without obvious ulceration or from a diverticulum) and perforation of preexisting sigmoid lesions (such as diverticulum or carcinoma), increased abdominal pain or exacerbation of the condition in patients with ulcerative colitis or Crohns disease (or the development of this condition), intestinal strictures and regional ileitis have been rarely reported. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). If gastro-intestinal bleeding does occur treatment with Indomethacin should be discontinued. Gastro-intestinal disorders which occur can be reduced by giving Indomethacin with food, milk or antacids. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

• *Hepato-biliary disorders:* cholestasis, borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT) have been seen in less than 1% of patients receiving therapy with NSAIDs in controlled clinical trials. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations such as rash or eosinophilia occur, Indomethacin should be stopped. Abnormal liver function, hepatitis and jaundice.

• *Skin and subcutaneous tissue disorders:* pruritus, urticaria, angioneurotic oedema, angiitis, erythema nodosum, rash, photosensitivity, exfoliative dermatitis, bullous reactions including Stevens Johnson syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity, erythema multiforme, hair loss, sweating and exacerbation of psoriasis.

• *Musculo-skeletal, connective tissue and bone disorders:* muscle weakness and acceleration of cartilage degeneration.

• *Renal and urinary disorders:* haematuria, nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure, renal insufficiency, proteinuria have all been reported. In patients with renal, cardiac or hepatic impairment, caution is required since the use of non-steroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored.

• *Reproductive system and breast disorders:* vaginal bleeding, breast changes (enlargement, tenderness, gynaecomastia)

• Clinical trial and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

a) Symptoms:

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

b) Therapeutic measure

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC CODE: M01A B01

Indomethacin is a non-steroidal anti-inflammatory agent with analgesic and antipytretic properties.

The analgesic properties have been attributed to both central and peripheral effect, which are distinct from its anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption: Indomethacin is readily absorbed from the gastrointestinal tract; peak plasma concentrations are reached in about 0.5-2 hours after a dose.

Distribution: More than 90% is bound to plasma proteins. It is distributed into synovial fluid, CNS and placenta. Low concentrations have been found in breast mik.

Metabolism: It is metabolised in the liver primarily by demethylation and deacetylation, it also undergoes glucuronidation and enterohepatic circulation. Half-life is between 3 – 11 hours.

Elimination: Mainly excreted in the urine, approximately 60%, the pH of the urine can affect this amount. Lesser amounts in the faeces. Indomethacin is also excreted in milk in small amounts.

5.3 Preclinical safety data

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

6. Pharmaceutical particulars

6.1 List of excipients

The capsules also contain: Starch; Powdered Cellulose ;Colloidal Silicon Dioxide;

Magnesium Stearate

The capsule shell contains: Yellow Iron Oxide ; Titanium Dioxide ; Gelatin

The printing ink contains: Shellac glaze ;Iron oxide black ; Propylene glycol

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf-life

Three years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Store below 25°C in a dry place.

Protect from light.

6.5 Nature and contents of container

Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side. Pack sizes: 10x10s,per box

Product may also be supplied in bulk packs As 1000capsule per bottle or Tin.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Ningbo Voice Biochemic Co., Ltd.

298 West Zhongshan Road, Ningbo, P.R. China