Summary of Product Characteristics

1. Name of the medicinal product

Indovis Capsules

2. Qualitative and quantitative composition

Indovis Capsules contain 25 mg of indomethacin
Excipient with known effect: Also contains lactose
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Indovis Capsules are white opaque capsules containing odorless white powder

4. Clinical particulars

4.1 Therapeutic indications

Non-steroidal anti-inflammatory indicated for the active stages of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, degenerative joint disease of the hip, acute musculoskeletal disorders, low-back pain.

4.2 Posology and method of administration

The dosage of Indovis should be carefully adjusted to suit the needs of the individual patient. In order to reduce the possibility of gastro-intestinal disturbances, *Indovis Capsules should always be taken with food or an antacid.*
In chronic conditions, starting therapy with a low dosage, increasing this gradually as necessary, and continuing a trial of therapy for an adequate period (in some cases, up to one month) will give the best results with a minimum of unwanted reactions.
The recommended oral dosage range is 50 mg to 200 mg daily in divided doses.
Paediatric dosage not established.
Use in the elderly: Indovis should be used with particular care in older patients who are more prone to adverse reactions.

4.3 Contraindications

- NSAIDs are contra-indicated 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.
- Hypersensitivity to indomethacin or any of the excipients listed in section 6.1.
- 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 or lactation (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 Indovis 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 Indovis.
Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Indovis 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).

- Indovis 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 Indovis 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.

- Indovis may mask the signs and symptoms of an infection. Indovis should be used with caution in patients with existing but controlled infection, so antibiotic therapy should be initiated promptly if an infection occurs during therapy with Indovis. It should be used with 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 at 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, hepatic, cardiac 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 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. Indovis should be given with caution and renal function should be monitored in patients (see also section 4.3).
  Discontinuation of non-steroidal anti-inflammatory 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.

- *Gastrointestinal bleeding, ulceration and perforation:*
  Caution is advised in patients with pre-existing sigmoid lesions (such as diverticulum or carcinoma) (or the development of these conditions) as Indovis can aggravate these conditions.
  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. When GI bleeding or ulceration occurs in patients receiving Indovis, 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 only 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 erythematous (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 Indovis 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 Indovis should be considered.

- Indovis should be used with caution in patients with coagulation defects as Indovis 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 Indovis.

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

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

- *Medication Overuse Headache (MOH):*
  After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH-medicationoveruse headache)

should be suspected in patients who have frequent or daily headache 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. Indovis should be discontinued at the first appearance of skin rash, mucosal lesions or 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.

- ***Fetal Toxicity***

  Premature Closure of Fetal Ductus Arteriosus:

  Avoid use of NSAIDs, including Indovis, in pregnant women at about 30 weeks gestation and later. NSAIDs, including Indovis, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

  Oligohydramnios/Neonatal Renal Impairment:

  Use of NSAIDs, including Indovis, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

  If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Indovis use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Indovis treatment extends beyond 48 hours. Discontinue Indovis if oligohydramnios occurs and follow up according to clinical practice [*see 4.6 Fertility, pregnancy and lactation*].

- *Excipient with known effect:*
  Indovis Capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

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).

- **Antacids:** the bioavailability of indomethacin may be reduced by concomitant antacid therapy

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

- **Anti-diabetics:** The effect of sulphonylureas may be increased by NSAIDs.

- **Antidepressants (SSRI):** increased risk of bleeding (see section 4.4)

- **Antihypertensive medications**: Reduced anti-hypertensive effect. Indovis 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 Indovis to the regimen of a patient taking any of the following antihypertensive agents: alpha-adrenergic blocking agents, ACE inhibitors, beta-adrenergic blocking agents, angiotensin II receptor antagonists, hydralazine, or nifedipine. An increased risk of hyperkalaemia has also been reported when NSAIDs are taken with ACE inhibitors.

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

- **Anti-platelet agents:** increased risk of gastrointestinal bleeding. Indovis can inhibit platelet aggregation, an effect which disappears within 24 hours of discontinuation; the bleeding time may be prolonged and this effect may be exaggerated in patients with an underlying haemostatic defect (see section 4.4).

- **Antipsychotics:** increased drowsiness with Indovis and haloperidol.

- **Antivirals:** Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
  Risk of Indovis 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 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). If the patient is receiving corticosteroids concomitantly, a reduction in dosage of these may be possible but should only be effected slowly under supervision.

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

- **Desmopressin:** effect potentiated by Indovis.

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

- **Lithium:** Decreased elimination of lithium.
  Indovis is an inhibitor of prostaglandin synthesis and therefore the following drug reaction may occur; Indovis may raise plasma lithium levels and reduce lithium clearance in subjects with steady state plasma lithium concentration. At the onset of such combined therapy, plasma lithium concentrations 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 plasma levels of indomethacin. When increases in the dose of Indovis are made under these circumstances, they should be made cautiously and in small increments.

- **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.

- **Salicylates:** the use of Indovis 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, coadministration of aspirin may decrease the blood concentrations of indomethacin

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

- **Tiludronic acid:** the bioavailability of tiludronic acid is increased by Indovis.

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

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

4.6 Fertility, Pregnancy and lactation

<u>pregnancy:</u>

Risk Summary:

Use of NSAIDs, including Indovis, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of Indovis use between about 20 and 30 weeks of gestation, and avoid Indovis use at about 30 weeks of gestation and later in

pregnancy (see Labor and Delivery - Clinical Considerations, Data).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including Indovis, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as Indovis, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Labor and Delivery

Clinical Considerations:

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including Indovis, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If Indovis treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Indovis and follow up according to clinical practice (*see Data*).

Data:

Human Data

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Lactation:

In the limited studies so far available, NSAIDs can appears in the 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, 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.

- *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, erythema multiforme).

- *Metabolic and nutrition disorders:*

Hyperglycaemia, glycosuria, hyperkalaemia has been reported rarely.

- *Nervous system disorders:*

Visual disturbances, optic neuritis, tinnitus, headaches, 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, dysarthia, 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 the therapy.

- *Eye disorders:*

Visual disturbances, blurred vision, diplopia, optic neuritis and orbital and peri-orbital pain are seen infrequently. Corneal deposits and retinal or macular disturbances have been reported in some patients with rheumatoid arthritis on prolonged therapy with Indovis. 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 oedema, hypertension, hypotension, tachycardia, chest pain, arrhythmia, palpitations, syncope and cardiac failure.

- *Vascular disorders:*

Flushing has been reported rarely.

- *Respiratory, thoracic and mediastinal disorders:*

Pulmonary eosinophilia. There may be bronchospasm in patients with a history of bronchial asthma or other allergic disease. Epistaxis has been reported rarely.

- *Gastrointestinal disorders*

The most commonly-observed adverse events are gastrointestinal in nature. Anorexia, epigastric discomfort, ulceration at any point in the gastro-intestinal tract (even with resultant stenosis and obstruction), bleeding (even without obvious ulceration or from a diverticulum) and perforation of pre-existing 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 Indovis should be discontinued.
Gastrointestinal disorders which occur can be reduced by giving Indovis 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, duodenal ulcer, gastric ulcer and gastrointestinal perforation have 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, Indovis should be stopped. Abnormal liver function, hepatitis and jaundice.

- *Skin and subcutaneous tissue disorders*:

Pruritus, urticaria, angioneurotic oedema, angiitis, erythema nodosum, skin rash and photosensitivity, exfoliative dermatitis, 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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, abdominal pain, anorexia, restlessness and agitation. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measures

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: M01AB01
Indovis is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties. The anti-inflammatory effect is due to inhibition of prostaglandin synthesis, which is does related and reversible.
The analgesic properties have been attributed to both a central and peripheral effect, which are distinct from its anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption: Indovis is rapidly and almost completely absorbed from the gastrointestinal tract; peak plasma concentrations are reached in about 0.5- 2 hours in fasting subjects, longer if taken with or after food.
Distribution: More than 90% is bound to plasma proteins. It is distributed into synovial fluid, CNS and placenta. Low concentrations have been found in breast milk. The concentration in synovial fluid is equal to that in plasma within 5 hours.
Indovis is largely converted to inactive metabolites.
Metabolism: It is metabolised in the liver primarily by demethylation and deacetylation, it also undergoes glucuronidation and enterohepatic circulation. Enterohepatic cycling of metabolites, and probably indomethacin itself, occurs. Half-life in plasma is variable from 2 – 11 hours.
Elimination: Mainly excreted in the urine, approximately 60%, the pH of the urine can affect this amount. Lesser amounts in the faeces. Indovis 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 the other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose, Cetyl Alcohol, Povidone, Titanium dioxide, gelatin

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C. Keep in original package.

6.5 Nature and contents of container

PVC/ aluminum foil blister packs contains 10 capsules per one blister. Each pack contains 20, 30, 100, 500, 1000 capsules in a cardboard box.
Not all pack sizes may be marketed

7. Manufacturer and Marketing authorisation holder

CTS Chemical Industries Ltd.
Hakidma 3
Kiryat-Malachi
Israel

8. Marketing authorisation number(s)

1324525943

9. Date of revision of the text

Revised in 06/2021 according to the MOH guidelines.