Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1.3Product Information

1.3.1 SPC, Labeling and Package Leaflet

SPC-Summary of Product Characteristics

Route of Administration: Oral Tablets

SPC-Summary of Product Characteristics

1. Name of the Medicinal Product

Ibuprofen Tablets BP 400mg

2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Ibuprofen BP 400 mg

Excipients Q.S

Colour: Erythrosine

3. Pharmaceutical Form

Film coated Tablet (For Oral Administration)

4. Clinical Particulars

4.1 Therapeutic Indications

Ibuprofen is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.

In the treatment of non-articular rheumatic conditions, Ibuprofen is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain; Ibuprofen can also be used in soft tissue injuries such as sprains and strains.

Ibuprofen is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for symptomatic relief of headache, including migraine headache.

Rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

Children under 12 years of age: Not recommended

4.2 Posology and Method of Administration

Posology

Adults, the elderly and children over 12 years:

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

1 or 2 tablets to be taken every four hours if necessary, up to three times a day, with or after food. Tablets should be swallowed with water. The dosage should not be repeated more frequently than every four hours and no more than 6 tablets should be taken in any 24 hour period.

Method of administration

For Oral Administration and short term use only.

4.3 Contraindications

Ibuprofen is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Ibuprofen should not be used in patients who have previously shown hypersensitivity reactions (e.g. asthma, urticaria, angioedema or rhinitis) after taking ibuprofen, aspirin or other NSAIDs.

Ibuprofen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Ibuprofen should not be used in patients with active, or history of, recurrent peptic ulcer or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.

Ibuprofen is contraindicated in patients with severe heart failure (NYHA Class IV), hepatic failure and renal failure .

Ibuprofen is contraindicated during the last trimester of pregnancy.

4.4 Special Warnings and Precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest possible duration necessary to control symptoms , and GI and cardiovascular risks below).

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

As with other NSAIDs, ibuprofen may mask the signs of infection.

The use of Ibuprofen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding .

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal .

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.

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 , and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 .

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

NSAIDs should be given with care to patients with a history of ulcerative colitis or Crohn's disease as these conditions may be exacerbated .

Respiratory disorders

Caution is required if Ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. $\leq$ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be

treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required..

Renal:

Renal impairment as renal function may further deteriorate

There is a risk of renal impairment in dehydrated adolescents.

Hepatic:

Hepatic dysfunction .

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 .

Dermatological effects

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 of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility

There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

The label will include:

Read the enclosed leaflet before taking this product.

Do not take if you:

• have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding

• are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers

• are taking other NSAID painkillers, or aspirin with a daily dose above 75mg

Speak to a pharmacist or your doctor before taking if you:

• have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems

• are a smoker

• are pregnant

If symptoms persist or worsen, consult your doctor.

4.5 Interactions with other medicinal products and other forms of interactions

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid:

Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardio protective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use .

Other analgesics and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs, including Cox-2 inhibitors, as this may increase the risk of adverse effects .

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDS may enhance the effects of anti-coagulants, such as warfarin (Special warnings and precautions for use).

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers and diuretics.

Diuretics can also increase the risk of nephrotoxicity of NSAIDs. Corticosteroids: May increase the risk of adverse reactions in the gastrointestinal tract including gastrointestinal ulceration or bleeding (See section 4.4 Special warnings and precautions for use).

Lithium: There is evidence for potential increases in plasma levels of lithium.

Methotrexate: There is a potential for an increase in plasma methotrexate.

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.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of

mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

Other analgesics and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs, including Cox-2 inhibitors, as this may increase the risk of adverse effects .

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.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding with NSAIDs

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

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

CYP2C9 Inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Cholestyramine; The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

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

4.6 Fertility, Pregnancy and Lactation

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses 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, Ibuprofen should not be given unless clearly necessary. If Ibuprofen is used by a woman attempting to conceive, or during the first or 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 the following:

Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)

Renal dysfunction, which may progress to renal failure with oligohydramnios.

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

Possible prolongation of bleeding time

Inhibition of uterine contractions, which may result in delayed or prolonged labour.

Consequently, Ibuprofen is contraindicated during the third trimester of pregnancy.

Lactation

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

Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

None expected at recommended doses and duration of therapy.

4.8 Undesirable Effects

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Immune System disorders:

Hypersensitivity reactions have been reported and these may consist of:

a) non-specific allergic reaction and anaphylaxis,

b) respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm dyspnoea

c) various skin reactions e.g. pruritis, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Uncommon: Hypersensitivity reactions with urticaria and pruritus.

Very rare: severe hypersensitivity reactions.

Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm.

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed

Gastrointestinal disorders:

Uncommon: abdominal pain, nausea and dyspepsia.

Rare: diarrhoea, flatulence, constipation and vomiting.

Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn's disease .

Unknown: pancreatitis

Cardiac disorders and vascular disorders:

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

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) .

Other adverse events reported less commonly and for which causality has not necessarily been established include:

Blood and lymphatic system disorders:

Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia

Psychiatric disorders: Insomnia, anxiety, depression, confusional state, hallucination

Nervous System disorders:

Uncommon: Headache.

Renal and urinary disorders:

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Unknown: Impaired renal function and toxic nephropathy in various forms, including interstitial nephritis and nephrotic syndrome

Hepatobiliary disorders:

Very rare: liver disorders.

Haematological:

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Skin and subcutaneous tissue disorders:

Uncommon: Various skin rashes

Very rare: Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Unknown: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and photosensitivity reaction

Infections and infestations:

Unknown: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation

Eye disorders:

Unknown: Visual impairment and toxic optic neuropathy

Ear and labyrinth disorders:

Unknown: Hearing impaired, tinnitus and vertigo

General disorders and administration site conditions:

Unknown: Malaise, fatigue.

General disorders and administration site conditions

Unknown : Malaise ,

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the

actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintainance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5.Pharmacological Properties

5.1 Pharmacodynamic Properties

ATC code – M01AE01

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID is thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardio protective effect of low-dose Acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetics

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

The half-life of Ibuprofen is approximately 2 hours.

In limited studies Ibuprofen appears in the breast milk in very low concentrations.

Ibuprofen is metabolised in the liver to two inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Ibuprofen is extensively bound to plasma proteins.

5.2 Pre Clinical Safety Data

No data of relevance, which is additional to that already, included in other sections of the SPC.

6 Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose
Maize starch
Gelatin
Methyl paraben
Propyl paraben
Purified water
Talcum
Sodium Starch Glycolate
Aerosil
Magnessium Sterate
Ready coat pink
Iso Propyl Alcohol
Methylene chloride

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 months from the Date of Manufacture

6.4 Special precautions for Storage

Store below 25°C

6.5 Nature and contents of Container

10 x 10 Tablets Alu-PVC

6.6 Special precautions for disposal

Not applicable

7. REGISTRANT

Merit Organics Ltd

Plot No 2104/2/A, G.I.D.C , Sarigam , Bhilad,

Dist- Valsad-396155, Gujarat , INDIA

8. MANUFACTURER

Merit Organics Ltd

Plot No 2104/2/A, G.I.D.C , Sarigam , Bhilad,

Dist- Valsad-396155, Gujarat , INDIA

9. DATE OF REVISION OF THE TEXT

Applicable once the registration is obtained.