

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral suspension contains 200 mg Ibuprofen.

Excipients with known effect

Maltitol liquid 2.5 g/5 ml and sodium 28.97 mg/5 ml oral suspension

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension

White to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term symptomatic treatment of mild to moderate pain.

For the short-term symptomatic treatment of fever.

4.2 Posology and method of administration

Posology

For pain and fever: The daily dosage of Easofen 200mg/5ml oral suspension for children is 20-30mg/kg bodyweight in divided doses. Using the measuring device provided this can be achieved as follows:

Child's age (weight)	Quantity and method of administration	Frequency (in 24 hour period)
6-9 years (20-30kg)	1 x 200ml/5ml (One 5 ml dose)	3 times
9-12 years (30-40kg)	1 x 300mg/7.5ml (5 ml + 2.5 ml)	3 times

Doses should be given approximately every 6 to 8 hours.

The package includes an oral syringe for oral administration of Easofen. The oral syringe is graduated in 0.25 ml steps up to 5 ml. 5 ml of oral suspension corresponds to 200 mg ibuprofen.

For patients with sensitive stomachs it is recommended that Easofen 200mg/5ml oral suspension is taken during a meal.

Not intended for children under 6 years of age or under 20kg.

Method of administration

For oral use.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4)

If in children aged from 6 years this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Special patient groups

Renal insufficiency: (see section 5.2)

No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic insufficiency: (see section 5.2).

No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with a history of bronchospasm, asthma, rhinitis or urticaria associated with the intake of acetylsalicylic acid or other non-steroidal anti-inflammatory medicinal products.
- Patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Patients with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Cerebrovascular or other active bleeding.
- Patients with severe hepatic failure, severe renal failure or severe heart failure (see section 4.4).
- Coagulation disorders (ibuprofen may increase bleeding time).
- Unclarified blood-formulation disturbances such as thrombocytopenia.
- Last trimester of pregnancy (see section 4.6).
- In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

4.4 Special warnings and precautions for use

Caution is required in patients with:

- Systemic lupus erythematosus as well as those with mixed connective tissue disease.
- Increased risk of aseptic meningitis (see section 4.8).
- Cardiac impairment (see section 4.5)
- A history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy (see section 4.3 and section 4.8).
- Renal impairment as renal function may further deteriorate (see section 4.3 and section 4.8).
- Hepatic dysfunction (see section 4.3 and section 4.8).
- Directly after major surgery.
- Hayfever, nasal polyps or chronic obstructive respiratory disorders as there is an increased risk in such patients of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.
- Previous allergic reactions to other substances, as there is an increased risk of hypersensitivity reactions occurring for such patients on use of this product.
- Congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Undesirable effects may be minimised by using the lowest effective doses for the shortest duration necessary to control symptoms (see gastrointestinal and cardiovascular risks).

Use with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided.

Elderly

The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Gastrointestinal Safety

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at any time during treatment, with or without symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses and 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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 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 stage 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 acetylsalicylic acid (see section 4.5).

When gastrointestinal 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 gastrointestinal or inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8)

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia, Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8)

Most of these reactions occurred within the first month.

If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Easofen 200mg/5ml oral suspension should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with cardiac impairment (see section 4.5) a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) and in long term treatment 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. 1200 mg daily) is associated with an increased risk of myocardial infarction.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Other notes

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of a hypersensitivity reaction after taking/administering Easofen Oral Suspension therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Ibuprofen, the active substance of Easofen Oral Suspension, may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Patients with coagulation disturbances should therefore be monitored carefully. NSAIDs should be used with caution in patients with idiopathic thrombocytopenic purpura (ITP), intracranial haemorrhage and bleeding diathesis.

Results of experimental investigations indicate an attenuation of the thrombocyte aggregation-inhibiting effect of acetylsalicylic acid on concomitant administration of ibuprofen. This interaction could reduce the desired protective cardiovascular effect of ASA. Ibuprofen should therefore only be used with particular caution in patients who are receiving ASA to inhibit thrombocyte aggregation (see section 4.5).

In prolonged administration of Easofen Oral Suspension, regular checking of the liver values, the kidney function, as well as of the blood count, is required.

On prolonged use of painkillers, headache may occur that must not be treated with increased doses of the medicinal product.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration therefore it should be avoided.

When using NSAIDs, concomitant consumption of alcohol may potentiate drug-related side effects, particularly those affecting the gastrointestinal tract or the central nervous system.

Adult patients taking non-steroidal anti-inflammatory painkillers, or acetylsalicylic acid with a daily dose above 75mg should avoid taking this medicine.

There is a risk of renal insufficiency in dehydrated children.

NSAIDs may mask symptoms of infection and fever.

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see Section 4.6).

Masking of symptoms of underlying infections:

Easofen Oral Suspension can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Easofen Oral Suspension is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Excipients

This medicinal product contains maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Maltitol may have a mild laxative effect. Calorific 2.3kcal/g maltitol.

This medicinal product contains 28.97 mg sodium per 5 ml, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Monitoring of clinical and biological parameters should be considered in patients taking ibuprofen concomitantly with the medicinal products listed below.

Concomitant use with the following medicinal products is not recommended

- Acetylsalicylic acid (Aspirin) (unless low dose acetylsalicylic acid (Aspirin) (not above 75mg daily) has been advised by a doctor),
- other NSAIDs (including cyclooxygenase-2 selective inhibitors) and
- glucocorticoids.

These may increase the risk of adverse reactions in the gastro-intestinal tract (see section 4.4).

Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly.

However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Precautions are required during concomitant use with the following medicinal products

- Diuretics, ACE inhibitors, beta-receptor blocking medicines and angiotensin-II antagonists:

NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, beta-receptor blocking medicine or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

The concomitant administration of Easofen Oral Suspension and potassium-sparing diuretics may lead to hyperkalaemia.

- Digoxin, phenytoin, lithium

The concomitant use of Easofen Oral Suspension with digoxin, phenytoin or lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium, serum-digoxin and serum-phenytoin levels is not as a rule required on correct use (maximum over 3 to 4 days).

- Methotrexate

There is evidence for the potential increase in plasma levels of methotrexate. NSAIDs inhibit the tubular secretion of methotrexate and decreased clearance of methotrexate may occur. For high-dose methotrexate treatment, ibuprofen (NSAIDs) should be avoided. The risk of an interaction between NSAIDs and methotrexate must also be considered with low dose methotrexate treatment, especially in patients with renal impairment. When methotrexate and NSAIDs are combined, the renal function should be monitored. Caution is advised if both NSAIDs and methotrexate are administered within 24 hours, as the plasma levels of methotrexate may increase and result in increased toxicity.

- Tacrolimus

The risk of nephrotoxicity is increased when both medicinal products are given concomitantly.

- Ciclosporin

There is limited evidence of a possible interaction leading to an increased risk of nephrotoxicity.

- Corticosteroids

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

- Anti-coagulants

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

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding (see section 4.4).

- Sulphonylureas

Clinical investigations have shown interactions between NSAIDs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as a precaution on concomitant intake.

- Zidovudine

There is evidence of an increased risk of haemarthrosis and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

- Probenecid and sulfinpyrazone

Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

- Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.
- Baclofen

Baclofen toxicity may develop after starting ibuprofen.

- Ritonavir

Ritonavir may increase the plasma concentrations of NSAIDs.

- Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

- 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.

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

Experimental studies indicate that ibuprofen inhibits the sodium excretion effect of captopril.

- Cholestyramine

At concomitant administration of ibuprofen and cholestyramine the absorption of ibuprofen is delayed and decreased (25%). The medicinal products should be administered with a few hours interval.

- Mifepristone

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis 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.

From the 20th week of pregnancy onward, Easofen Oral Suspension use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Easofen Oral Suspension should not be given unless clearly necessary. If Easofen Oral Suspension 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Easofen Oral Suspension for several days from gestational week 20 onward. Easofen Oral Suspension should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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, Easofen Oral Suspension is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

Fertility

There is some evidence that active substances which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

For short-term use this medicinal product, has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and vary inter-individually. The following frequencies are taken as a basis when evaluating undesirable effects:

Very common: $\geq 1/10$	Common: $\geq 1/100$ to $< 1/10$
Uncommon: $\geq 1/1,000$ to $< 1/100$	Rare: $\geq 1/10,000$ to $< 1/1,000$
Very rare: $< 1/10,000$	Not known: cannot be estimated from the available data

The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients. The stated frequencies, which extend beyond very rare reports, refer to the short-term use of daily doses up to a maximum of 1200 mg ibuprofen for oral dosage forms and a maximum of 1800 mg for suppositories (=30ml oral suspension of Easofen 200mg/5ml Oral Suspension maximum daily dose for adults and children older than 12 years).

Infections and infestations

Very rarely, exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.

If signs of an infection occur or get worse during use of Easofen 200mg/5ml Oral Suspension, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy.

Very rarely, the symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.

In exceptional cases, severe skin infections and soft tissue complications may occur during a varicella infection

Blood and lymphatic system disorders

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding. In such cases, the patient should be advised to discontinue this medicinal product, to avoid any self-medication with analgesics or antipyretics and to consult a physician.

The blood count should be checked regularly in long-term therapy.

Immune system disorders

Uncommon: hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure).

The patient is to be instructed to inform a doctor at once and no longer to take Easofen 200mg/5ml Oral Suspension in this case.

Very rare: severe general hypersensitivity reactions. They may present as face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening shock.

Not known: Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea.

If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.

Psychiatric disorders

Very rare: psychotic reactions, depression.

Nervous system disorders

Uncommon: central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness.

Very rare: Aseptic meningitis

Eye disorders

Uncommon: visual disturbances.

Ear and labyrinth disorders

Rare: tinnitus.

Cardiac disorders

Very rare:

- Palpitations, heart failure, myocardial infarction.
- Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Not known:

- Kounis Syndrome

Clinical trial and epidemiological data suggest that the use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Vascular disorders

Very rare: arterial hypertension, vasculitis.

Respiratory, Thoracic and Mediastinal Disorders

Very rare: Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.

Gastrointestinal

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, 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.

Common: gastro-intestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.

Uncommon: gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis.

Very rare: oesophagitis, pancreatitis, formation of intestinal, diaphragm-like strictures.

The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.

Hepatobiliary disorders

Very rare: hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis, cholestatic jaundice, elevation of serum enzymes.

Skin and subcutaneous tissue disorders

Uncommon: skin rash

Very rare:

- Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)
 - Alopecia
 - Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.
 - Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella.

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions.

Renal and urinary disorders

Very rare:

- Decrease of urea excretion, oedema can occur, particularly in patients with arterial hypertension.
- Also, renal insufficiency, nephritic syndrome, interstitial nephritis that may be accompanied by acute renal failure is possible.
- Papillary necrosis especially in long term use.
- Increased serum urea concentrations.

Investigations:

Very rare: Haemoglobin decreased, urea renal clearance decreased

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 national reporting system:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

In children risk of toxic effects should not be excluded with a dose above 100mg/kg. In adults the dose response effect is less definitive. In serious poisoning metabolic acidosis may occur.

Symptoms of overdosing

The symptoms of overdose can include nausea, vomiting, diarrhoea abdominal pain, headache, dizziness, drowsiness, nystagmus, blurred vision, tinnitus, gastrointestinal bleeding and, rarely, hypotension, metabolic acidosis, renal failure and loss of consciousness. In more serious poisoning toxicity is seen in the central nervous system, manifesting as dizziness, drowsiness, occasionally excitation and disorientation, loss of consciousness or coma.

Occasionally patients develop convulsions. In serious poisoning hyperkalaemia and metabolic acidosis, may occur and the prothrombin time/INR may be prolonged, probably due to the interference with the actions of circulating clotting factors. Acute renal failure liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

Therapeutic measure in overdosing

No specific antidote is available.

Management should be symptomatic and supportive and include the management of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal or gastric emptying if the patient presents within one hour of ingestion of a potentially toxic amount. If ibuprofen has already been absorbed, alkaline substances may be administered to promote the excretion of acid ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma. The local poisons centre should be contacted for medical advice.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non steriods: propionic acid derivatives

ATC code: M01AE01

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

The clinical efficiency of ibuprofen has been demonstrated in the symptomatic treatment of mild to moderate pain such as pain through toothache, headache, and in the symptomatic treatment of fever.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are used concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusion can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

No special studies on pharmacokinetics have been carried out in children. Literature data confirm that the absorption, metabolism and elimination of ibuprofen in children proceeds in the same way as in adults.

After oral administration ibuprofen is partly absorbed in the stomach and afterwards completely in the small intestine. After hepatic metabolism (hydroxylation, carboxylation, conjugation) the pharmacologically inactive metabolites are eliminated completely, mainly renally (90 %), as well as via the biliary route. The elimination half life for healthy persons as well as for patients suffering from hepatic or renal diseases is 1.8 to 3.5 hours. Plasma protein binding is about 99 %.

Renal impairment

Since ibuprofen and its metabolites are primarily eliminated by the kidneys, patients with varying degrees of renal impairment may display altered pharmacokinetics of the drug. For patients with renal impairment decreased protein binding, increased plasma levels for total ibuprofen and unbound (S)- ibuprofen, higher AUC values for (S)- ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported. In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see also section 4.3)

Hepatic impairment

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters. Hepatic disease can alter the disposition kinetics of ibuprofen. In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)- ibuprofen to the active (S)- enantiomer (see also section 4.3).

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments showed up mainly in form of lesions and ulcerations in the gastro-intestinal tract. *In vitro* and *in vivo* studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found.

Ibuprofen inhibited ovulation in rabbits and led to implantation disorders in various animal species (rabbit, rat, mouse). Experimental studies in rat and rabbit have shown that ibuprofen crosses the placenta. Following administration of maternotoxic doses, an increased incidence of malformations (ventricular septal defects) occurred in the progeny of rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Maltitol
Citric Acid anhydrous
Sodium Citrate

Sodium benzoate (E211)

Sodium Chloride

Sodium Saccharin

Hypromellose

Xanthan gum

Strawberry Flavour (natural flavouring preparations, maize maltodextrin, triethyl citrate (E1505), propylene glycol (E1520) and benzyl alcohol)

Glycerol (E422)

Thaumatococcus (E957)

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

After first opening, store below 25°C. Use within 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber coloured polyethylene terephthalate (PET) bottles of 30 ml, 100, 150 and 200ml with a child-resistant closure, fitted with a low density polyethylene stopper.

The product is supplied with a 5 ml oral syringe, comprising of a high-density polyethylene piston and a polypropylene barrel. The oral syringe is graduated in 0.25 ml steps up to 5 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Shake the bottle before use

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd

Waterford Road

Clonmel, Co. Tipperary

E91 D768

Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/060/004

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