Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brupro for Children 100 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral suspension contains 100 mg ibuprofen.

Excipients with known effect: maltitol liquid (500 mg/ml) and sodium (3.59 mg/ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.

Off-white oral suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Brupro for Children is used for the short-term symptomatic treatment of:

- mild to moderate pain
- fever.

Brupro for Children is for use in children from 5 kg body weight (3 months) to 39 kg body weight (11 years)

4.2 Posology and method of administration

Posology

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

The dosage is in line with the details in the following table. In children, Brupro for Children is dosed depending on body weight (BW), as a rule with 7 to 10 mg/kg BW as a single dose to a maximum of 30 mg/kg BW as the total daily dose.

The respective dosing interval should be chosen in line with the symptomatology and the maximum daily dose. It should not be below 6 hours. The recommended maximum daily dose should not be exceeded.

Body weight (Child's age)	**Quantity ibuprofen (method of administration)**	**Frequency in 24 hours (max. daily ibuprofen dose)**
5-6kg (3-8 months)	1 x 50mg/2.5ml (using the syringe once)	3 times (150mg)
7-9kg (9-11 months)	1 x 50mg/2.5ml (using the syringe once)	3 to 4 times (150-200mg)
10-15kg (1-3 years)	1 x 100mg/5ml (using the syringe once)	3 times (300mg)

16-19kg (4-5 years)	1 x 150mg/7.5ml (using the syringe twice: 5ml+2.5ml)	3 times (450mg)
20-29kg (6-9 years)	1 x 200mg/10ml (using the syringe twice: 2x5ml)	3 times (600mg)
30-39kg (10 -11 years)	1 x 300mg/15ml (using the syringe thrice: 3x5ml)	3 times (900mg)

If symptoms worsen or persist for longer than 3 days, a doctor should be visited.

Patients with renal impairment (see section 4.4 and 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).

Patients with hepatic impairment (see section 4.4 and 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).

Paediatric population:
Not intended for use in children below 5 kg body weight or below 3 months of age.

For infants aged 3-5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist.

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

Method of administration
The package includes a 5 ml oral syringe (graduated in 0.25 ml steps up to 5 ml).

For oral administration and short-term use only.

The bottle has to be shaken vigorously before use.

The oral suspension can be taken without regard to meals. People with a sensitive stomach are recommended to take Brupro for Children during meals.

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, angioedema or urticaria after taking acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients with unclarified blood-formation disturbances such as thrombocytopenia.
Patients with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding.

Patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Patients with cerebrovascular or other active bleeding.

Patients with severe impairment of liver or kidney function or severe heart failure (NYHA Class IV).

Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

Pregnant patients, during the last three months of pregnancy.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).

Gastrointestinal safety
The use of Brupro for Children with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime 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 (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 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 acetylsalicylic acid (see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

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 daily) 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 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.

Skin reactions
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. Brupro for Children 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 Brupro for Children in case of varicella.

Other notes:
Brupro for Children should only be used with strict assessment of the benefit/risk ratio:
- in systemic lupus erythematosus (SLE) and mixed connective-tissue disease – increased risk of aseptic meningitis (see section 4.8).
- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)

Particularly careful monitoring by a doctor is required:
- in impaired renal function (as an acute deterioration of the renal function can occur in patients with pre-existing renal disease);
- in dehydration
- in hepatic dysfunction;
- directly after major surgical procedures;
- in patients who suffer from hayfever, nasal polyps, chronic swelling of the nasal mucosa or chronic obstructive respiratory disorders, as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria;
- in patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of Brupro for Children.

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of ahypersensitivity reaction after taking/administering Brupro for Children, therapy must be stopped. Medically required measures, inline with the symptoms, must be initiated by specialist personnel.

Respiratory disorders: Caution is required if Brupro for Children is administered to patients suffering from, or with a previoushistory of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Patients with coagulation disturbancesshould therefore be monitored carefully.

In prolonged administration of Brupro for Children, regular checking of the liver values, the kidney function, as well as of theblood count, is required.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medicaladvice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should besuspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, maylead to permanent renal damage with the risk of renal failure (analgesic nephropathy).

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern thegastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

NSAIDs may mask symptoms of infection and fever.

Adequate hydration should be ensured, as dehydration can lead to renal insufficiency when ibuprofen is given.

This medicinal product contains 2.34 mmol (or 53.85 mg) sodium per highest single dose of 15ml.

Brupro for Children contains maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take thismedicine.

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 themedicinal products listed below.

Concomitant use with the following medicinal products is not recommended:

Other NSAIDs and glucocorticoids:
These may increase the risk of adverse reactions in the gastro-intestinal tract.

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 theyare dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to theclinical situation, the possibility that regular long-term use of ibuprofen may reduce the cardioprotective effect of low dose acetylsalicylic acid cannot be excluded. No clinically relevant effect isconsidered 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, betareceptor 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, betareceptor 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.

The concomitant administration of Brupro for Children and potassium-sparing diuretics may lead to hyperkalaemia.

Digoxin, phenytoin, lithium:
The concomitant use of Brupro for Children 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 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).

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 haemarthroses 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.

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:
A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs.
Limited evidence suggests that co-administration 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development.

Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation 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.

During the first and second trimester of pregnancy, Brupro for Children should not be given unless clearly necessary. If Brupro for Children is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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

- the fœtus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
- the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occureven at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Brupro for Children is contraindicated during the third trimester of pregnancy (see section 4.3).

Breastfeeding

Ibuprofen and its metabolites pass only in low concentrations into the breast milk. Since harmful effects to infants have not become known to date, an interruption of breast-feeding is usually not necessary during short-term treatment with ibuprofen at the recommended dose (see section 4.2).

Fertility

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.

4.7 Effects on ability to drive and use machines

If taken as recommended, ibuprofen has no or negligible influence on the ability to drive and use machines.

As central nervous undesirable effects such as tiredness and dizziness may occur on use of ibuprofen at higher dosage, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The listing of undesirable effects below comprises all side effects reported during treatment with ibuprofen, including those reported during high-dose long-term therapy in patients with rheumatic disorders. Reported frequencies other than very rare reports refer to short-term use of daily doses of up to 1200mg ibuprofen (= 60 ml Brupro for Children) for oral formulations and a maximum of 1800 mg for suppositories.

The assessment of side effects is based on the following frequency classification:
Very common: ≥1/10
Common: ≥1/10 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and varyinterindividually.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimesfatal, 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) havebeen reported following administration. Less frequently, gastritis has been observed. Particularly the risk of gastrointestinalbleeding occurring is dependent on the dose range and the duration of use.

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

Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke)(see section 4.4).

Infections and infestations
Very rare: exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use ofnon-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidalanti-inflammatory drugs.

If signs of an infection occur or get worse during use of Brupro for Children, the patient is therefore recommended to go to adoctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy.

Very rare: the symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness cloudinghave been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to bepredisposed.

Blood and lymphatic system disorders
Very rare: disturbances to blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis).

The first signs may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding. In such cases, the patient should be advised to discontinue the medicine immediately, 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 Brupro for Children 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.

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.

Eye disorders
Uncommon: visual disturbances. In this case, the patient should be instructed to inform the doctor immediately and to discontinue ibuprofen.

Ear and labyrinth disorders
Rare: tinnitus.

Cardiac disorders
Very rare: palpitations, heart failure, myocardial infarction.

Vascular disorders
Very rare: arterial hypertension.

Respiratory, thoracic and mediastinal disorders
Very rare: asthma, bronchospasm, dyspnoea and wheezing

Gastrointestinal disorders
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 relatively 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.

Skin and subcutaneous tissue disorders
Uncommon: various skin rashes
Very rare: bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell’s syndrome), alopecia.

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").

Renal and urinary disorders
Rare: renal tissue damage (papillary necrosis), particulary in long-term therapy, increased serum uric acid concentration in the blood.
Very rare: reduced urinary excretion and formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency.

Renal function should therefore be checked regularly.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of an overdose
Symptoms include central nervous disturbances such as headache, dizziness, light-headedness, loss of consciousness (also myoclonic convulsions in children), as well as, abdominal pain, nausea and vomiting. In addition, gastrointestinal bleeding, as well of functional disturbances of the liver and kidneys, is possible. There may furthermore be drop in blood pressure, respiratory depression or cyanosis.

Therapeutic measures in overdose
There is no specific antidote to ibuprofen.

The therapeutic possibilities for treatment of intoxication are dictated by the extent, level and clinical symptoms according to the common measures of intensive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids; Propionic acid derivatives
ATC code: M01AE01

Ibuprofen is a non-steroidal anti-inflammatory drug that, in the conventional animal-experiment inflammation models, has provento be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen has an antipyretic effect, reduces inflammatory-relatedpain and swelling. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregationwhen they are dosed concomitantly. Some pharmacodynamics studies show that when single dose of ibuprofen 400mg weretaken within 8 h before orwithin 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acidon the formation ofthromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolationof these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded.No clinicallyrelevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

On oral application, ibuprofen is already partly absorbed in the stomach and then completely in the small intestine. Peak plasma levels following oral administration of a normal-release pharmaceutical form are reached after 1−2 hours. Following hepatic metabolisation (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90 %), but also with the bile. The elimination half-life in healthy individuals and those with liver and kidney diseases is 1.8 − 3.5 hours, plasma-protein binding about 99 %.

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 impaired implantation 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

Sodium benzoate (E211)
Citric acid anhydrous
Sodium citrate
Saccharin sodium
Sodium chloride
Hypromellose
Xanthan gum
Maltitol liquid
Glycerol (E422)
Strawberry flavor (flavourings identical to natural substances, flavouring preparations, maltodextrin (maize based), E1505 triethyl citrate, E 1520 propylene glycol, added benzyl alcohol)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening: 6 months.
Store below 25ºC.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/225/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 07th March 2014

10 DATE OF REVISION OF THE TEXT

July 2016