Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Buplex Junior 100mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is ibuprofen.
5 ml of oral suspension contains 100 mg of ibuprofen.

Excipients with known effect:
5 ml of oral suspension contains 2 g of maltitol liquid.
5 ml of oral suspension contains 7.370 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

White to almost white suspension with orange-vanilla flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Children 3 months to 12 years (> 5 kg):

- the reduction of fever, including post immunisation pyrexia
- the relief of the symptoms of colds and influenza
- the relief of mild to moderate pain, such as a sore throat, teething pain, toothache, earache, headache, minor aches and sprains.

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).

Children from 3 months of age

For post immunisation pyrexia: One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

For pain, fever and symptoms of cold and influenza: The daily dosage of Buplex Junior 100mg/5ml Oral Suspension is 20-30 mg/kg bodyweight in divided doses. Using the oral dosing syringe provided this can be achieved as follows:

Infants 3 – 6 months weighing more than 5 kg: One 2.5ml dose may be taken 3 times in 24 hours.
Infants 6 - 12 months (7 – 10 kg): One 2.5 ml dose may be taken 3 to 4 times in 24 hours.
Children 1 - 3 years (10 – 15 kg): One 5 ml dose may be taken 3 times in 24 hours.
Children 4 - 6 years (15 – 20 kg): 7.5 ml may be taken 3 times in 24 hours.

Children 7 - 9 years (20 – 30 kg): 10 ml may be taken 3 times in 24 hours.
Children 10 - 12 years (30 – 40 kg): 15 ml may be taken 3 times in 24 hours.

Doses should be given approximately every 6 to 8 hours, (or with a minimum of 6 hours between each dose if required).

Infants under 3 months of age or weighing less than 5 kg should not take Buplex Junior 100mg/5ml Oral Suspension due to lack of data on safety and efficacy.

Duration of treatment
For short-term use only.
Children aged over 6 months: If symptoms worsen or persist for more than 3 days, consult a doctor.
Children aged under 6 months: If symptoms worsen or persist for more than 24 hours, seek medical advice.

Renal impairment
Caution should be taken with ibuprofen dosage in patients with renal impairment. The dosage should be assessed individually. The dose should be kept as low as possible and renal function should be monitored (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Caution should be taken with dosage in patients with hepatic impairment. The dosage should be assessed individually and the dose should be kept as low as possible (see sections 4.3, 4.4 and 5.2).

Method of administration

For oral administration.
Shake well before use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- 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.
- Severe hepatic or severe renal insufficiency
- Severe heart failure (NYHA Class IV)
- Last trimester of pregnancy (See section 4.6)
- Conditions involving an increased tendency to bleeding

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 GI and cardiovascular risks below).

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

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

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

Other NSAIDs:

The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8 Undesirable effects)..

Renal:
Renal impairment as renal function may further deteriorate (See section 4.3 Contraindications and Section 4.8 Undesirable effects)
Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, those taking diuretics or ACE-inhibitors and the elderly. Monitoring of renal function is necessary, especially in high risk patients.
There is a risk of renal impairment in dehydrated children and adolescents.

Hepatic:
Hepatic dysfunction (See section 4.3 Contraindications and Section 4.8 Undesirable effects)

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. ≤ 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.

Gastrointestinal bleeding, ulceration and perforation:
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).

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 (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 medicinal products 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 ibuprofen, the treatment should be withdrawn.

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. Ibuprofen 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 tissue 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 (see section 4.8).

Other precautions:
Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

Due to the presence of maltitol liquid in the composition of Buplex Junior, patients with rare hereditary problems of fructose intolerance should not take this medicine.
Maltitol liquid may have a mild laxative effect.
Each 5 ml spoonful contains 2 g of maltitol liquid. This provides 4.6 kcal per 5 ml spoonful.

This medicinal product contains 7.37 mg of sodium in each 5 ml dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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 cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of gastrointestinal ulcers and haemorrhage (see section 4.4).

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

Anti-platelet aggregation agents: Increase the risk of gastrointestinal bleeding (see section 4.4).

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.

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.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of

hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate, leading to an increased risk of toxic effects. NSAIDs should therefore not be taken by patients receiving high-dose treatment with methotrexate (also see below).

Cardiac glycosides: NSAIDs may exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside (e.g. digoxin) levels.

Ibuprofen should be used with caution in combination with:

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of antihypertensives, such as ACE inhibitors, beta-blockers and diuretics.
Diuretics can increase the risk of nephrotoxicity of NSAIDs.
The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

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

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Aminoglycosides: NSAIDs may reduce the excretion of aminoglycosides.

Lithium: NSAIDs can increase the serum level of lithium, by reducing renal excretion of lithium.

Methotrexate: The risk of a potential interaction between an NSAID and methotrexate should also be taken into account in connection with low-dose treatment with methotrexate, especially in patients with renal impairment. Whenever combination treatment is given, renal function should be monitored. Caution should be exercised if both an NSAID and methotrexate are given within 24 hours of one another, as the plasma levels of methotrexate may increase, resulting in increased toxicity (also see above).

Ciclosporin: The risk of kidney damage is increased.

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

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

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.

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

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydramniosis;

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 ibuprofen is contraindicated during the last trimester of pregnancy.

Lactation:
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 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

Since side effects such as dizziness and visual disturbances may be experienced, the ability to drive a car or operate machinery may be impaired.

4.8 Undesirable effects

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, heamatemesis, ulcerative stomatits, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Assessment of adverse reactions is normally based on the following occurrence frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations
Very rare: 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 Ibuprofen the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for anti-infective/antibiotic therapy.

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, unexplained bleeding and bruising.

Immune system disorders
Uncommon: Hypersensitivity reactions (e.g urticaria, pruritus, and exanthema as well as asthma attacks and hypotension).
Rare: Lupus erythematosus syndrome.

Very rare: Severe hypersensitivity reactions (e.g. facial oedema, swelling of the tongue, internal laryngeal swelling, dyspnoea, tachycardia, fall in blood pressure (life-threatening shock)). Bronchospasm

Nervous system disorders
Common: Headache, dizziness.

Eye disorders
Rare: Visual disturbances.

Cardiac disorders and Vascular disorders
Not known: 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 (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Gastrointestinal disorders
Very common: Abdominal pain, nausea, dyspepsia.
Common: Gastrointestinal ulcers.
Rare: Diarrhoea, flatulence, constipation and vomiting.
Very rare: Perforation or gastrointestinal bleeding, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Hepatobiliary disorders
Very rare: Liver disorders, hepatitis.

Skin and subcutaneous tissue disorders
Very rare: Severe forms of skin reactions such as exfoliative and bullous dermatoses, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis.
Not known: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also *"Infections and infestations"*). Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome).

Vascular disorders
Very rare: Hypertension.

Renal and urinary disorders
Uncommon: Renal failure
Very rare: Papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

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

In children, ingestion of more than 100 mg/kg may cause symptoms. Ingestion of more than 400 mg/kg may cause a

serious toxic reaction.
In adults, the dose response effect is less clear cut.
The half-life in overdose is 1.5 to 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 maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying or oral administration of activated charcoal is indicated 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

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives.
ATC code: M01AE01.

Ibuprofen is a propionic acid derivative NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase. In addition ibuprofen has an inhibitory effect on ADP (adenosine diphosphate) or collagen-stimulated platelet aggregation.

Ibuprofen has been shown to have an onset of both analgesic and antipyretic action within 30 minutes.

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 waere 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 cardioprotective effect of low-dose acetysalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Ibuprofen inhibits prostaglandin synthesis in the uterus, thereby reducing intrauterine rest and active pressure, the periodic uterine contractions and the amount of prostaglandins released into the circulation. These changes are assumed to explain the allevation of menstrual pain. Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients (see section 4.3).
Prostaglandins are connected with ovulation and the use of medicinal products inhibiting prostaglandin synthesis may therefore affect the fertility of women (see section 4.4, 4.6 and 5.3).

5.2 Pharmacokinetic properties

Absorption
Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occur one to two hours after administration. If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach. Food does not affect markedly total bioavailability.

Distribution
Ibuprofen is rapidly distributed throughout the whole body. Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.

Biotransformation
Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.

Elimination
The elimination half-life is approximately 2.5 hours in healthy individuals. Pharmacologically inactive metabolites are mainly excreted (90%) by the kidneys but also in bile.

Special populations

Elderly
Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between young and elderly.

Children
The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults. Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age.

Renal impairment
For patients with mild renal impairment increased 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 sections 4.2, 4.3 and 4.4).

Hepatic impairment
Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen 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 sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

As a well established and widely used product, the pre-clinical safety of ibuprofen is well documented.

Ibuprofen's subchronic and chronic toxicity was mainly shown by animal tests as gastric tract damage and ulcers.

The vitro and in vivo tests have not shown any clinically significant signs about ibuprofen's mutagenicity. Furthermore no carcinogenic effects have been observed in mice and rats.
Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species (rabbit, rat, and mouse). In reproduction tests undertaken with rats and rabbits, ibuprofen passed across the placenta. When using doses toxic to the mother, malformations occur more frequently (i.e. ventricular septum defects).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)
Citric acid anhydrous
Maltitol liquid
Xanthan gum
Hypromellose
Glycerol
Sodium chloride
Polysorbate 80
Sodium cyclamate
Acesulfame potassium
Sucralose
Orange flavour (Orange Juice 055604 TEU) containing:
- Flavouring components (flavouring preparations, flavouring substances, natural flavoring substances)
- Alpha-tocopherol (E307)
- Benzyl alcohol

Vanillin
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
Shelf life after first opening the bottle: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Buplex Junior 100mg/5ml Oral Suspension is supplied in an amber glass bottle containing 60 ml, 100 ml or 200 ml, or an amber PET bottle containing 100 ml. The bottle is closed with a child-resistant HDPE screw cap with a PP outer cap and a PE adaptor.
Each pack also contains an oral dosing syringe with a capacity of 5 ml and marked with dosing graduations every 0.5ml. Each syringe consists of a PP syringe body and an HDPE plunger.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76 – 78
220 Hafnarfjördur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/087/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th June 2015

10 DATE OF REVISION OF THE TEXT

April 2018