SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CHILDREN'S IBUFEN 100 mg/5 mL pediatric suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL contains 100 mg ibuprofen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Suspension.

Orange coloured, orange-flavoured suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children

CHILDREN'S IBUFEN Pediatric Suspension:

- For the short term in order to decrease pyrexia in children aged 6 months and aged over 6 months,
- For the short term in order to treatment slightly and moderate aches in children aged 6 months and aged over 6 months,
- Treatment for Juvenil rheumatoid arthritis symptom

4.2 Posology and method of administration

Posology/Administration Frequency and Duration:

For children

20- 30 mg/kg body weight in daily divided doses. Using the spoon or syringe dosing device provided this can be achieved as follows:

Age	**Dose**	**Period**
6 month – 1 year (if more than 7 kg)	2.5 ml (50mg)	3 times in daily
1-2 years old	2.5 ml (50mg)	3-4 times in daily
3-7 years old	5 mL (100 mg)	3-4 times in daily
8-12 years old	10 mL (200 mg)	3-4 times in daily

Doses should be given 4 times every 6 hours later.

In the indication of juvenile rheumatoid arthritis, can be used until 40 mg/kg/day body weight in daily divided doses.

Adults

Proposed dose divided doses is 1200-1800 mg. In some patients, continue in 600-1200 mg/day. If dose is increased until stop of acute phase in severe and acute cases, it can be advantage. Daily dose should not be more than 2400 mg divided doses So if necessary dose can be increased to 3200 mg. In this status, patient should be monitored, closely.

Unexpected effects can be decreased by using with short term the effective lowest dose to control the symptoms (see. section 4.4).

Method of administration

For oral administration.

Treatment with CHİLDREN'S IBUFEN, burning sensation can be in mouth or throat. Shake oral suspension well before using.

Additional information on special populations:

Renal/Hepatic/Heart Impairment: Caution is required prior to starting treatment in patients with a history of renal, hepatic and/or heart failure, renal function disorder have been reported in association with Non-Steroid anti-inflammatory NSAII therapy. In these patients, dose should be stable in the lowest level and monitored the renal functions.

Pediatric Population:

Not recommend in children not less than 7 kg.

Geriatric Population: If renal or hepatic function disorders to adjust dosage as personally are not, special dose modification is not necessary. Caution with dose. Dose should be adjusted as personally. The lowest effective dose should be used in the shortest time.

The elderly may be more sensitive effects of NSAIDs. Especially, gastrointestinal bleeding anperforation can be mortal.

4.3 Contraindications

Hypersensitivity to ibuprofen or any of the excipients in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.
Last trimester of pregnancy.

Severe hepatic failure.

Severe renal failure (glomerular filtration <30 ml/min.)

Increase bleeding.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
A history of gastrointestinal disease (ulcerative colitis, Crohn's disease, recurrent peptic ulcer or haemorrhage) (two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure.

Before and after term coroner artery bypass surgery.

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 Posology and administration, GI and cardiovascular risks below).

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

Caution is required prior to CHILDREN'S IBUFEN starting treatment in patients with a history of peptic ulceration and other gastrointestinal failure, because of heartburn.

Caution is required prior to starting treatment in patients with a history of renal, hepatic and/or heart failure, renal failure have been reported in association with NSAID therapy. To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration and monitored renal function.

Caution 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 ibuprofen therapy.

CHİLDREN'S IBUFEN can be masked infection symptoms as other NSAID.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAIDs therapy.

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

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of the patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal:

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 gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as other NSAID includes cyclo-oxygenase-2 (COX-2) selective inhibitors. Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin
Increased adverse reaction against to MSAID drugs in elderly patient (Especially, gastrointestinal bleeding and perforation can be mortal).

If gastrointestinal bleeding or ulceration consists in patient with treatment ibuprofen, treatment should be stopped.

Renal

Caution is required prior to ibuprofen treatment in patient with important dehydration.
Long-term ibuprofen administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.
Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ADE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Hematologic effects:

Ibuprofen may be inhibited thrombocyte aggregation like NSAIDs and bleeding time may be increased.

Respiratory:

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

Aseptic Meningitis:

Aseptic meningitis has been observed on rare occasions in patients on ibuprofen as found in ibuprofen. Although it is probably more likely to occur in patients with systemic lupus erythematous and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Dermatological:

Serious skin reactions, some of them fatal, including exfoliate dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrosis, have been reported very rarely in association with the use of NSAIDs. 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.

The Drug Product contains sodium less than 1 mmol (23 mg) each dose; therefore it does not contain sodium.

This medical product contains 1.5 g glucose in each 5 mL. Caution in patients with diabetes mellitus patients. Also, not recommend patients with rare genetical galactose intolerance, Lapp lactose impairment, glucose-galactose malabsorption problem, rare genetical fructose intolerance or sucrose-isomaltase impairment.

This medical product contains 0.5 g sorbitol in each 5 mL. Not recommend in patients with rare genetical fructose intolerance problem. Sorbitol can be caused discomfort in fundus and diarrhea.

CHILDREN'S IBUFEN contains glycerine. Glycerine can be caused headache, discomfort in fundus and diarrhea in high doses.

Small a group human can be caused allergic with E110 or sodium benzoate. Allergic reaction are rare but allergic reaction with E110 in human has got allergic with aspirin is common. Do

not use CHILDREN'S IBUFEN in allergic human with aspirin. Sodium benzoate can be decreased the risk of hepatitis in newborn.

So, allergic reactions can be consisted allergic reactions because of parahydroxybenzoate.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be used with caution in combination with:

Anticoagulants (dicumarole group, warfarin): Experimental studies have been shown that ibuprofen is strengthen effects on bleeding time of warfarin.

Ticlopidine: NSAID do not use with ticlopidine because of inhibition of thrombocyte function.

Methotrexate: NSAIDs, has been reported to competitively inhibit methotrexate tubular secretion. There is a potential for an increase in plasma methotrexate. Caution should be used when NSAID is administered concomitantly with methotrexate.

Aspirin (Acetylsalicylic acid): Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin 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 the regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

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

Mifepristone: The efficacy of medical product can reduce due to prostaglandin property of NSAIDs. Treatment NSAIDs with prostaglandin in the same day have not been effected as negatively the effects on cervical ripening of mifepristone or prostaglandin and pregnancy termination is not reduce clinical efficacy.

Sulphonilure: NSAIDs can be potentialized on the effect of sulphonilure group drugs. Hyphlisemi has been reported with ibuprofen treatment in patients treatment with sulphonire.

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.

Alcohol: Do not use with ibuprofen and alcohol concomitantly because increase the important gastrointestinal adverse effects like bleeding.

Other analgesics: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects.

Ibuprofen may be adjusted dose with caution in combination with:

Anti-hypertensive (ADE inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and drugs used in pulmonary hypertension (endotelyn receptor antagonists, bosentan)): NSAIDs can reduce antihypertensive effect (See section 4.4). When used NSAIDs includes COX-2 selective inhibitors with ADE inhibitors and angiotensin-II antagonists concomitantly, increased risk of serious renal impairment as reversible in patients with renal (e.g. dehydrate or elderly patients). Therefore, caution the combination in patients with renal impairment especially elderly patients. Patients should be hydrated after combination treatment and during treatment, periodically and control renal function (see section 4.4).

Diuretics (thiazide, thiazide diuretics and loop diuretics) can increase the risk of nephrotoxicity of NSAIDs. NSAIDs can inhibit the diuretic effect of furosemide and bumetanidin

Due to inhibition of prostaglandin synthesis. So, it can be reduced the effect of thiazides antihypertensive.

Aminoglycosides: NSAIDs can reduce elimination of aminoglycosides. (especially in preterm babys).

Lithium: Ibuprofen has been shown to produce an elevation of plasma lithium levels and a reduction in renal lithium clearance. Avoid the combination if plasma lithium levels do not control and not reduce lithium dose. NSAIDs can reduce elimination of lithium.

Selective serotonin reuptake inhibitors, SSRIs (e.g. paroxetine, fluoxetine, sertraline): Increased risk of gastrointestinal bleeding SSRI and NSAID as well as. Increased the risk

with combination treatment. This mechanism is related with reduce reuptake in the thrombocyte of serotonin (see section 4.4.).

Cyclosporine: Increased risk of nephrotoxicity because of decreasing prostacyclin synthesis in renal. Therefore, monitored renal function as closely in combination treatment.

Captopril: Experimental studies have been shown that ibuprofen effects adverse in effect of sodium elimination of captopril.

Colestiramine: Delayed and decreased ibuprofen absorption in treatment with İbuprofen and kolestiraminin, concurrently. (at ratio of 25%). The drugs should be take every 2 hours.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. In order to decrease prostacycline synthesis in renal, possible increased risk of nephrotoxicity after administration NSAIDs and tacrolimus concurrently. Therefore, renal function should be closely monitored during combination treatment.

Methotrexate: There is a potential for an increase in plasma methotrexate in patients with renal impairment. Monitored renal function as closley in combination treatment. Caution should be used when NSAID is administered concomitantly with methotrexate within 24 hours.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Antitrombositic agents (e.g. clopidogrel): Increased risk of gastrointestinal bleeding.

CYP2C9 Inhibitors: Increased ibuprofen exposure (CYP2C9 substrate) with treatment with CYP2C9 inhibitors ibuprofen (CYP2C9 substrate). Increased S(+)-ibuprofen exposure in the ratio of 80-100 % in the study done with voriconazole and fluconazole (CYP2C9 inhibitors), Especially, ibuprofen dose can be reduced if treatment the high dose ibuprofen with potent CYP2C9 inhibitors like voriconazole or fluconazole

Herbal extracts: Ginkgo biloba can be potential bleeding risk with NSAID.

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.

Interaction studies have been only done in adults.

4.6 Fertility, pregnancy and lactation

General Recommendation

Pregnancy category: C/D (3. trimester).

Women of Childbearing Potential/Contraception

If ibuprofen is used during the first and second trimester of pregnancy due to the potential, dose to be applied should be low and the treatment period should be very short period.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embrio-fetal development. Data obtained from epidemiological studies cause a concern about an increased risk of abortion and cardiac malformation after use of prostaglandin synthesis inhibitors in early stage of pregnancy. In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations including cardiovascular malformations have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis.

Ibuprofen is not recommend during first and second trimester, if not very necessary. If ibuprofen is used during the first and second trimester of pregnancy due to the potential, dose to be applied should be low and the treatment period should be very short period.

In third trimester of pregnancy, all prostaglandin synthesis inhibitors can be caused below combination:

- Cardiopulmonary toxicity (premature closure of ductus arteriosus and pulmonary hypertension);
- Renal dysfunction to be caused renal impairment with Oligohydramniose

In third trimester in pregnancy, all prostaglandin synthesis inhibitors in mother and newborn can be caused below combination:

- Increases bleeding time
- Uterus contractions inhibition to be result with delayed or extension labour

Labour and delivery may be delayed. The duration increased with an increased bleeding tendency in both mother and child.

In conclusion, ibuprofen is contraindicated during third trimester.

Lactation

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely. Ibuprofen is nor recommend in the nursing mother.

Female Fertility

Ibuprofen can effect adversely fertility. No recommend in pregnancy due to the potential. Ibuprofen may cause impairment of female fertility by an effect on ovulation. Stop ibuprofen treatment in females.

4.7 Effects on ability to drive and use machines

None expected at recommended doses and duration of therapy.

Adverse effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. The patients affected due to these effects should not drive or use machine.

4.8 Undesirable effects

The following adverse reactions for oral ibuprofen are similar with other NSAIDs

They are listed by System Organ Class and ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) including isolated reports.

SYSTEM ORGAN CLASS	Frequency	Undesirable Effects
Infections and infestations	Uncommon	Rhinitis
	Rare	Aseptic meningitis reports (especially in patients with autoimmune disorders such as systemic lupus erythematous, mixed type tissue disorders), neck stiffness, headache, nausea, vomiting, pyrexia and orientation disorders
Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.
Metabolism and nutrition disorders	Rare	Anaphylactic reaction
Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.
Psychiatric disorders	Uncommon	Insomnia, Anxiety
	Rare	Depression, confusion, hallucinations
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Parestezi
	Rare	Optical neuritis, Somnolence
Eye disorders	Uncommon	Visual disturbance
	Rare	Toxic optic neuropathic
Ear and labyrinth disorders	Uncommon	Hearing disorders
	Rare	Tinnitus, vertigo
Respiratory, thoracic and mediastina disorders	Uncommon	Asthma, Bronchospasm Dyspnoea
Gastrointestinal disorders	Common	Dyspepsia, Diarrhoea,

		Nausea, Vomiting Abdominal pain, Flatulence, Constipation melaena, hematemesis, gastrointestinal haemorrhage
	Uncommon	Gastric, duodenal ulcer, gastric ulcer, oral ulceration
	Rare	Gastrointestinal perforation
	Very rare	Pancreatic
	Unknown	Colit and Crohn syndrome
Hepatobiliary disorders	Uncommon	Hepatic, hepatitis, hepatic function disorder
	Rare	Hepatic disorder
	Very rare	Hepatic impairment
Skin and subcutaneous tissue disorders	Common	Skin rash
	Uncommon	Exfoliate, pruritus, urticarial, angioedema, photosensitivity reactions
	Rare	Stevens Johnson syndrome Toxic epidermal necrolysis erythema multiform
Renal and urinary disorders	Uncommon	Tubular interstisyel Nephritis, nephrotoxic syndrome and renal impairment
General disorders and administration site conditions	Common	Slackness
	Rare	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 EFDA

yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Toxicity

Toxicity symptoms are generally observed for doses less than 100 mg/kg in children or adults. However, supportive treatment may be necessary in some cases. Toxicity symptoms and signs are observed in children after oral administration of 400 mg/kg dose or more doses.

Symptoms

The symptoms are headache, nausea, vomiting, epigastria pain, gastrointestinal bleeding, diarrhea rarely, orientation disorders, excitation, coma, drowsiness, dizziness, tinnitus, syncope and sometimes convulsions.

Acute renal insufficiency and hepatic damage are possible in significant poisoning cases.

Shown symptoms within 4-6 hours in patient with taking important amounts ibuprofen

Common; symptoms, vomiting, nausea, abdominal pain, lethargy and dizziness.

Central nervous system symptoms; dizziness, headache, tinnitus, convulsion and sensory loss. Rarely; nistagmus metabolic acidosis, hypothermic, renal effects, gastrointestinal bleeding, coma, apne and CNS and respiratory system depression. Cardiovascular toxicity symptoms like hypotension, bradycardia and tachycardia

If treatment with other drugs, overdose generally tolerate.

Treatment

Symptomatic treatment should be performed according to the clinical condition of patients when accidental or excessive intake. Recommend to use active carbon within 1 hour after excretion potential toxic amounts. Alternatively in adults, recommend to use gastric lavage within 1 hour after taking overdose.

Urination should be carried. Renal and hepatic functions should be closely monitored. Patients should be kept under observation at least 4 hours after taking potentially toxic amounts of the drug.

Convulsions, seen frequently or continued for a long time, should be treated with intravenous diazepam. Other precautions may be considered according to the clinical condition of the patients.

Consult the nearest toxic information center to reach current data.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs
ATC code: M01AE01

Ibuprofen is propionic acid derivate that analgesic, anti-inflammatory and antipyretic activities. Therapeutic effects of ibuprofen is a result non-selective inhibitor effect on cyclooxygenase izo enzymes (COX-1 and COX-2). Ibuprofen has been consisted the signed decreasing in synthesis of prostaglandin.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin 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 conclusions 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

General Properties

Absorption

Absorption:
Ibuprofen is absorbed with bioequivalence in the ratio of 80-90 % in gastrointestinal canal, speedly. After administration, the Cmax is reached at range 1-2 hours. When administered concomitantly with food, the AUC does small than hungry and its absorption rate is delayed. Food is not affected total bioavailability.

Ibuprofen bind in the big ratio (99%) and distribution volume in adults are about 0.12-0.2 L/kg

Distribution:

As with other drugs with high plasma protein binding (99 %), mean value of the distribution volume is less than 0.12-0.2 L/kg.

Biotransformation

Ibuprofen to metabolize with CYP2C9 sitocrom P450 in kidney as 2-hydroxyibuprofen and 3-carboxyibuprofen which are two primer inactive metabolite, speedly. After administration as orally, an amount less than 90 % of ibuprofen is shown oxidative metabolites in urinary and glucuronide conjugation of these. The very small amount of ibuprofen does not change and excretion.

Elimination

The elimination half life ranges 2 hours. The main elimination of ibuprofen is completed within 24 hours.

Special Populations

Elderly

Observed only minor, differences not identified as clinically between young and elderly patients in pharmacokinetic profile and urinary elimination if no renal impairment.

Children

Shown to similar ibuprofen exposure the adjustment dose according to weight in children 1 year and above the ages (5 mg/kg and 10 mg/kg body weight) with adults. Shown the distribution volume (L/kg) and clearance (L/kg/sa) more in children between 3 months – 2.5 years than children 2.5-12 years

Renal Impairment

The average free fraction of ibuprofen is about 3 % in patients with severe renal impairment and about 1 % in the healthy volunteers. Severe renal impairment may cause to collect ibuprofen metabolites. The mean of effect is not known. Metabolites may remove with haemodialysis (see section 4.2, 4.3 and 4.4)

Hepatic Impairment:

The single dose and repeated doses in volunteers with alcoholic hepatic disorder with moderate hepatic impairment, the mean differences is not shown as statistical in the pharmacokinetic parameters.

Observed half life is extension average 2 times and decrease enantiomer AUC ratio (S/R) in the mean ratio according to the healthy volunteers treatment racemic ibuprofen in cirrhosis patients (Child Pugh score 6-10), with moderate hepatic impairment. This status has been shown that decrease metabolic recovery (R)-ibuprofen to active (S)-enantiomer (see section 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Acute toxicity:

Species	**Sex**	**Dose range mg/kg**	**Non-effective max. level mg/kg**	**Effective min. dose mg/kg**	**Max. non-letal dose mg/kg**	**Min. letal dose mg/kg**	**Non-fetal max. dose mg/kg**
Mause (oral)	E	200-1600	200	400	200	400	800
Mause (ip)	E	100-1600	100	200	100	200	800
Rat (oral)	E	400-1600	400	800	800	1600	1600
Rat (sc)	E	400-1600	800	1600	800	1600	1600

Chronic toxicity:

Observed gastrointestinal system ulceration as individual continuous pathologic symptom. The lowest doses in symptoms: 300 mg/kg in mouse; 180 mg/kg in rat; 100 mg/kg in monkey; 8 mg/kg in dog. The level of gastrointestinal non-damaged has been found as 60 mg/kg in day with 6 months period in rat and 75 mg/kg in day with 90 days period. At the end of 2 years, renal papillary changes have been found in rat. The symptoms are type for non-steroidal anti-inflammatories and are suspect the significance in human.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerin

Xanthan gum

Sodium benzoate

Sodium citrate dihydrate

Citric acid anhydrous

Sodium saccharin dihydrate

Sodium chloride

Polysorbate 80

Microcrystalline cellulose-Carboxymethyl cellulose sodium

Sucrose

Sorbitol (E420)

Orange flavor

Sunset yellow (E110)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30 oC at the room temperature. Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Amber coloured 100 mL glass bottle, polyethylene cap, 5 mL polyethylene spoon and leaflet in cartoon box.

6.6 Special precautions for disposal <and other handling>

No special requirements.

Any used product or waste material should be disposed of in accordance with “Regulation of Control of Medical Waste” and “Regulation of Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORISATION HOLDER

Name and address:BİLİM İLAÇ SAN. ve TİC. A.Ş.

Kaptanpaşa Mah. Zincirlikuyu Cad. No:184

34440 Beyoğlu-ISTANBUL

Phone: +90 (212) 365 15 00

Fax: +90 (212) 276 29 19

8. MARKETING AUTHORISATION NUMBER(S)

Certificate No: 05804/07755/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Mar 23, 2021

10. DATE OF REVISION OF THE TEXT

September 2023