SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
IBURAMIN ZERO 100 mg/1 mg/5 ml suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml (1 spoon) suspension contains;

Active substances:

Ibuprofen	100 mg
Chlorpheniramine maleate	1 mg

Excipients:

Sorbitol (70%) (E420)	125 mg
Sucrose	1,875 g
Sodium benzoate (E211)	5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Suspension
Almost white colored, suspension with characteristic odor (strawberry)

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
It is indicated to eliminate or reduce the symptoms of cold, flu and viral upper respiratory tract infections.

4.2. Posology and method of administration
Posology/frequency of administration and duration of the treatment:
Unless otherwise recommended by doctor, it is used as follows;

5 ml in children aged 2-4 years
7,5 ml in children aged 4-6 years
10 ml in children aged 6-12 years

When necessary, the dose is repeated every 6-8 hours (3-4 times a day). It should not be used more than 4 doses per day.

Undesirable effects can be minimized by using the lowest effective dose required to control symptoms as soon as possible (See Section 4.4).

Method of administration
It is taken by mouth.

Ensure that the bottle is shaken well before use

Additional information for special populations
Renal/Hepatic/Cardiac failure:
Caution should be exercised in patients with renal, hepatic or hearth failure, because the use of NSAIDs such as ibuprofen can lead to impairment in renal functions. In these patients, dose should be kept as low as possible and renal function should be monitored. It can cause undesirable sedation in patients with severe liver disease. It should not be used in patients with hepatic failure.

Pediatric population:
It is contraindicated in children under 2 years.

Geriatric population:
The frequency of undesirable effects such as gastrointestinal (Gİ) bleeding and perforation that may be fatal with use of NDAIDs in this patient group is increased.

Thus, if NSAIDs ~~needs~~ are required to use in elderly patients, the possible lowest effective dose and the shortest duration of treatment should be preferred.

It should be used under medical supervision in patients older than 65 years of age. These individuals are more susceptible to neurological, anticholinergic effects. The maximum daily dose should not exceed 12 mg for chlorpheniramine maleate.

4.3. Contraindications
- It is contraindicated in children under 2 years.
- Hypersensitivity to ibuprofen, chlorpheniramine or any of the excipients in the product,
- Patients who have previously showed allergic reactions such as asthma, urticaria against aspirin or other NSAIDs,
- Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy,
- Patients with active or history of ulcerative colitis, Crohn's disease, recurrent peptic ulcer or gastrointestinal hemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding),
- Patients with bleeding tendency,
- Patients with severe cardiac failure (NHYHA Class IV),
- Patients with severe hepatic failure,
- Patients with severe renal failure (Glomerular filtration < 30 ml/min),
- Patients in the period of pre or post-coronary artery bypass surgery,
- Third trimester of pregnancy.
- Patients taking monoamine oxidase inhibitors (MAOI) within the last 14 days.

4.4. Special warnings and precautions for use

Cardiovascular (CV) Risk
- NSAIDs may cause increased risk of cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

- İBURAMİN ZERO is contraindicated for treatment of peri-operative pain management in the setting of coronary artery by-pass surgery.

Gastrointestinal (GI) risks
NSAIDs cause serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These adverse events can occur at any time with or without prior warning symptoms. Elderly patients are at a greater risk for serious gastrointestinal events.

It is contraindicated in children under 2 years.

To minimize the undesired effects, the lowest effective dose for management of the symptoms should be used for the shortest possible duration (see section 4.2 and below-mentioned gastrointestinal and cardiovascular risks).

İBURAMİN ZERO should be used with caution in patients with bronchial asthma or preexisting bronchial asthma, since it has been reported that ibuprofen causes bronchospasm in such patients.

İBURAMİN ZERO should be given with care to patients with a history of peptic ulceration and other gastrointestinal diseases, as these conditions may be exacerbated.

Caution is also required in patients with renal, hepatic or cardiac impairment since use of NSAIDs may result in deterioration of renal function. Dose levels should be kept as low as possible and renal function should be monitored in such patients.

Caution is required when administering İBURAMİN ZERO in patients with a history of heart failure or hypertension as edema cases associated with ibuprofen therapy have been reported.

As with the other NSAIDs, İBURAMİN ZERO may mask the symptoms of infection.

Cardiovascular effects:

Cardiovascular Thrombotic Events:
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Physicians

and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if such events occur.

There is no consistent evidence that concurrent use of aspirin mitigates the risk of serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of aspirin and NSAIDs does increase the risk of serious GI events.

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following coronary artery bypass surgery found an increased incidence of myocardial infarction and stroke.

Clinical studies have shown that use of ibuprofen, particularly at high doses (2400 mg / day), may be associated with a small increase in the risk of arterial thrombotic events (eg, myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low-dose ibuprofen (eg <1200 mg / day) may be associated with an increased risk of myocardial infarction.

Hypertension:

NSAIDs including İBURAMİN ZERO, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

NSAIDs, including İBURAMİN ZERO, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema:

Fluid retention and edema have been observed in some patients taking NSAIDs. İBURAMİN ZERO should be used with caution in patients with fluid retention or heart failure.

Patients with uncontrolled hypertension, congestive heart failure (NYHA Class II-III), current ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and avoiding high doses (2400 mg / day).

Particularly when high doses of ibuprofen (2400 mg / day) are required, patients with risk factors for cardiovascular events (e.g., hypertension, hyperlipidemia, diabetes, smoking) should also be carefully evaluated before a long-term treatment is initiated.

<u>Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation</u>

NSAIDs, including İBURAMİN ZERO, can cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper gastrointestinal adverse event on NSAID therapy, is symptomatic. Upper gastrointestinal ulcers, bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of

developing a serious gastrointestinal advers reactions at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a gastrointestinal bleeding compared to patients treated with neither of these risk factors. Other factors that increase the risk of gastrointestinal bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal gastrointestinal events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse gastrointestinal event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of gastrointestinal ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal event is suspected. NSAID therapy should be even discontinued until a serious gastrointestinal adverse event is ruled out. For high-risk patients, alternative therapies that do not involve NSAIDs should be considered.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing ibuprofen doses, in patients with a history of ulcer (particularly if complicated with hemorrhage or perforation) and in the elderly. These patients should commence treatment on the lowest dosepossible. 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.

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) in the initial stages of treatment.

When gastrointestinal bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

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

Renal Effects

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathological changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandins formation and, secondarily, in renal blood flow, which may accelerate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those who are taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy usually results in recovery to the pre-treatment state

Advanced Renal Failure

No information is available from controlled clinical studies regarding the use of İBURAMİN ZERO in patients with advanced renal disease. Therefore, treatment with İBURAMİN ZERO is not recommended in these patients with advanced renal disease. If İBURAMİN ZERO therapy must be initiated, close monitoring of the patients renal function is advisable.

Anaphylactic Reactions

As it is for other NSAIDs, anaphylactoid reactions may occur in patients who were not known to be exposed to İBURAMİN ZERO previously. İBURAMİN ZERO should not be given to patients with Aspirin triade. This symptom complex typically develops in asthma patients having rhinitis, with or without nasal polyp or in patients showing potential fatal, serious bronchospasm after taking aspirin or other NSAIDs.

Ocular Effects

In trials, no ocular changes that would be caused by ibuprofen administration was shown. In rare cases, undesired ocular disorders as papillitis, retrobulber optical neuritis and papilledema were reported by patients using NSAIDs including Ibuprofen, but the relation with cause and effect could not be established; thus ophthalmologic examination should be made in patients developing eye disorder during ibuprofen treatment.

Hepatic effects

Up to 15% of patients receiving NSAIDs, including IBURAMIN ZERO, elevation to the upper limit in one or more liver tests may occur. These laboratory anomalies may progress, remain unchanged, or spontaneously resolve when the treatment is continued. In clinical studies with NSAIDs, significant increases in ALT and AST activities (three times or more of the upper limit of the normal level) were reported in approximately 1% of patients. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and liver failure, some of which have resulted in death, have also been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction during treatment with IBURAMIN ZERO. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), IBURAMIN ZERO treatment should be discontinued.

Hematological effects

In patients receiving NSAIDs including İBURAMİN ZERO, anemia may be observed. The reason of that is liquid retention, hidden or apparent GI blood loss or not completely defined effects on erythropoiesis. For patients on long-treatment with NSAIDs including İBURAMİN ZERO, hemoglobin and hematocrit values should be controlled if they exhibit any sign or symptoms of anemia.

It is shown that NSAIDs inhibit the platelet aggregation and increases the bleeding time in some patients. Unlike aspirin, their effects on platelet functions are quantitatively less, for a short time and reversible. As patients with clotting disorder or patients receiving anti-coagulants, patients treated with İBURAMİN ZERO that are negatively affected by the changes in platelet functions should be carefully monitored.

Pre-existing Asthma

Patients with asthma may have asthma sensitive to aspirin. In patients having asthma sensitive to aspirin, usage of aspirin is associated with severe bronchospasm which may be fatal. In such patients sensitive to aspirin, as cross reactions were reported among aspirin and other NSAIDs including bronchospasm, İBURAMİN ZERO should not be used and it should be used with caution for patients having pre-existing asthma.

Aseptic Meningitis

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

Dermatological Effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at the highest risk of 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.

Also use of İBURAMİN ZERO should be avoided in case of the following conditions;

- Arrhythmias
- Serious hypertension
- Cardiovascular diseases
- Epilepsy
- Prostatic hypertrophy
- Hepatic impairment
- Glaucoma
- Bronchitis, bronchiectasis, asthma
- Overactive thyroid dysfunction.

Children and the elderly are more susceptible to neurological anticholinergic side effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness).

As it contains sorbitol (E420) and sucrose, patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not use this medicine.

Each dose (5 ml) contains 1,875 g sucrose. This should be considered in patients with diabetes (diabetes).

Because this medicine contains polyoxyl 40 castor oil, it can cause nausea and diarrhea.

This medicinal product contains less than 1 mmol (23 mg) of sodium per 5 ml; that is, it does not actually contain sodium.

It may cause allergic reactions due to ponso 4R (E124) in its composition.4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised in patients being treated with any of the following drugs as interaction has been reported in some patients. Combined use of İBURAMİN ZERO and the following agents should be avoided. Dose adjustments may be required when used with the following agents

Ibuprofen:
Combined use of İBURAMİN ZERO and the following agents should be avoided:
Anticoagulants (dicumarol group, warfarin): Experimental studies have demonstrated that ibuprofen potentiates the effects of warfarin on bleeding time. NSAIDs and dicumarol derivatives are metabolized by the same enzyme (i.e. CYP 2C9). NSAIDs may increase the effect of anticoagulants such as warfarin.

Ticlopidine: NSAID-products should not be combined with ticlopidine because of inhibition of platelet function.

Methotrexate: The risk of a potential interaction between an NSAID and methotrexate should 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, as the plasma levels of methotrexate can increase, resulting in increased toxicity.

Aspirin (Acetylsalicylic acid): As with other products containing NSAIDs, co-administration of acetylsalicylic acid and ibuprofen is not recommended due to the increased potential for adverse effects. Experimental data show that, when used concurrently, ibuprofen can competitively inhibit the effect of low-dose acetylsalicylic acid on platelet aggregation. Although there is uncertainty about the clinical extrapolation of these data, the possibility that long-term and continuous use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. A clinically significant effect with occasional ibuprofen is unlikely to be observed (see section 5.1).

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

Mifepristone: A decrease of the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs including acetylsalicylic acid. 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 and does not reduce the clinical efficacy of medical termination of pregnancy.

Sulphonylureas: NSAIDs may potentiate the effects of sulphonylurea medications. There are rare reports of hypoglycaemia in patients on sulphonylurea medications receiving ibuprofen.

Zidovudine: There may be an increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hematoma and hemarthroses in HIV(+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Alcohol: Concomitant take of ibuprofen and alcohol should be avoided as it may increase the risk of important gastrointestinal side effects such as bleeding.

Other analgesics: Concomitant use of two or more NSAIDs should be avoided.

Concomitant use of ibuprofen with the following agents may require dose adjustment:
Antihypertensives (ACE inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and medications for pulmonary hypertension (endothelin receptor antagonists, bosentan): NSAIDs can decrease antihypertensive effect (See. Section 4.4). When NSAIDs, including selective COX-2

inhibitors are concomitantly administered with ACE inhibitors and angiotensin II receptor antagonists, there is an increased risk of acute renal failure (which is usually reversible) in patients with renal impairment (e.g. dehydrated or elderly patients). Therefore, for the patients with compromised renal function, especially the elderly, this combination should be administered with caution. Patients should be adequately hydrated and monitoring of renal function is recommended after initiation of combination therapy and periodically thereafter during the treatment (See. Section 4.4).

Diuretics (thiazides, thiazide like diuretics and loop diuretics) can also increase the risk of nephrotoxicity of NSAIDs. NSAID-drugs can reduce the diuretic effect of furosemide and bumetanide, possibly by inhibiting prostaglandin synthesis. They can also decrease the antihypertensive effect of thiazides.

Aminoglycosides: NSAIDs may reduce the excretion of aminoglycosides (especially in preterm babies).

Lithium: Ibuprofen reduces renal clearance of lithium, as a result of a decrease in serum lithium levels. Combination should be avoided if frequent controls of serum lithium levels and potential reduction of lithium dose cannot be done. NSAIDs may decrease elimination of lithium.

Selective serotonin reuptake inhibitors, SSRIs (e.g. paroxetine, fluoxetine, sertraline): SSRI and NSAID each involve an increased risk of bleeding e.g. from the gastrointestinal tract. This risk increases at concomitant treatment. The mechanism may be associated with a decreased uptake of serotonin in the thrombocytes (see section 4.4).

Cyclosporine: It is presumed that administering of NSAIDs concomitantly with cyclosporine may increase the risk of nephrotoxicity because of decreased prostacyclin synthesis in kidney. Therefore in case of combination treatment renal function must be closely monitored.

Captopril: Experimental studies indicate that ibuprofen counteracts the effect of captopril on increased sodium excretion.

Cholestyramine: The concomitant administration of ibuprofen and cholestyramine retards and reduces (by 25%) the absorption of ibuprofen. These drugs should be taken at least 2 hours apart.

Tacrolimus: When NSAIDs are co-administered with tacrolimus, possible increased risk of nephrotoxicity may be expected. It is presumed that administering of NSAIDs concomitantly with tacrolimus may increase the risk of nephrotoxicity because of decreased prostacyclin synthesis in kidney. Therefore, in case of combination treatment renal function must be closely monitored.

Corticosteroids: May increase the risk of gastrointestinal ulceration or bleeding, when co-administered with the NSAIDs.

Anti-platelets (e.g. clopidogrel): Increased risk of gastrointestinal bleeding is likely to occur, when combined with the NSAIDs.

CYP2C9 Inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole, an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the

ibuprofen dose should be considered, particularly when high-dose ibuprofen is administered concomitantly with potent CYP2C9 inhibitors such as voriconazole or fluconazole.

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

Quinolone derivative antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolone may have increased risk of developing convulsions. The interaction studies have been conducted only in adults.

Chlorpheniramine maleate:
When alcohol and classic antihistaminics (with sedative effects) are co-administered, sedative effect is enhanced. Sedative interactions apply to a lesser extent to the non-sedating antihistamines. Interactions do not generally apply to antihistamines used for topical action (including inhalation).

Caution must be exercised when using with epilepsy drugs containing phenytoin, medications for anxiety or sleep regulation.

Additional information for special populations:
No interaction studies have been performed on special populations.

Pediatric population:
No interaction studies have been performed on the pediatric population.

4.6. Pregnancy and lactation

General advise
Pregnancy category is C (D at the 3rd trimester).

Women of Childbearing Potential/Birth control (Contraception)
If ibuprofen would be used by a woman attempting to conceive, or during the first and second trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

There are no adequate data for the use of chlorpheniramine in pregnant women, the potential risk in humans is unknown. Use during the third trimester may result in reactions in the newborn or premature neonates, therefore it should not to be used during pregnancy unless considered essential by a physician.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo/fetal 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 trimesters of pregnancy, İBURAMİN ZERO should not be given unless clearly necessary. If İBURAMİN ZERO is used by a woman attempting to conceive, or during the first and second

trimesters 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 fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension),
- renal dysfunction, which may progress to renal failure with oligohydramnios

the mother and the neonate, at the end of pregnancy, to:

- prolongation of bleeding time
- inhibition of uterine contractions resulting in delayed or prolonged labor

Consequently, İBURAMİN ZERO is contraindicated during the third trimester of pregnancy.

Lactation
Based on data from limited clinical studies, like all NSAIDs, ibuprofen appears in the breast milk in very low concentrations. Chlorpheniramine maleate is excreted in the breast milk in significant amounts. Chlorpheniramine maleate and other antihistamines may inhibit lactation.
Therefore, use of IBURAMIN ZERO is not recommended in lactating women whenever possible.

Fertility
The use of ibuprofen may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

Chlorpheniramine had no effects on fertility in rats and rabbits at oral doses approximately 20 to 25 times the maximum recommended human dose on a mg/m2 basis.

4.7. Effects on ability to drive and use machines
İBURAMİN ZERO may cause undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances. If such undesirable effects occur, patients should be warned not to drive or operate machinery.

4.8. Undesirable effects
The adverse reactions reported have been listed by the following frequency (very common (≥ 1/10); common (≥ 1/100 to< 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10.000 to < 1/1000); very rare (< 1/10.000), not known (cannot be estimated based on available data).

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

Blood and lymphatic system disorders:
Rare: Leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia, hemolytic anemia and blood dyscrasias

Immune system disorders:
Rare: Anaphylactic reaction
Not known: Allergic reactions and angioedema

Nervous system disorders:
Very common: Sedation and somnolence
Common: Headache, dizziness, distractibility and abnormal coordination
Uncommon: Paresthesia
Rare: Optic neuritis
Very rare: Seizure
Not known: Tremor

Eye disorders:
Common: Blurred vision
Uncommon: Visual impairment
Rare: Toxic optic neuropathy

Ear and Labyrinth disorders:
Uncommon: Hearing impaired
Rare: Tinnitus and vertigo

Respiratory, thoracic and mediastinal disorders:
Uncommon: Asthma, bronchospasm, dyspnea
Not known: thickening of bronchial secretion

Gastrointestinal disorders:
Common: Dyspepsia, diarrhea, nausea, vomiting, abdominal pain, flatulence, constipation, melena, hematemesis, gastrointestinal hemorrhage
Uncommon: Gastritis, duodenal ulcer, gastric ulcer, oral ulceration, gastrointestinal perforation
Rare: Dry mouth
Very rare: Pancreatitis
Not known: Colitis and Crohn's disease

Hepato-biliary disorders:
Uncommon: Hepatitis, jaundice, hepatic dysfunction
Rare: Hepatic damage
Very rare: Hepatic impairment

Skin and subcutaneous tissue disorders:
Common: Skin rash
Uncommon: Urticaria, pruritus, purpura, angioedema, photosensitivity
Very rare: bullous skin inflammation including Stevens-Johnson's syndrome, toxic epidermal necrolysis and erythema multiform
Not known: Exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

Renal and urinary tract disorders:
Uncommon: tubule interstitial nephritis, nephrotic syndrome and renal impairment
Rare : Urinary retention

General disorders and administration site conditions:
Uncommon: Fatigue
Rare: Edema

Musculo-skeletal and connective tissue disorders:
Not known: Muscular twitching, muscle weakness

Edema, hypertension and heart failure have been reported in association with non-steroidal anti-inflammatory therapy. Clinical trials 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 (e.g. myocardial infarction or stroke) (see Section 4.4).

The most common adverse effects are seen with the GI system. Particularly in the elderly, ulcers, perforation or bleeding may be sometimes fatal. Following ibuprofen administration, nausea, vomiting, diarrhea, indigestion, constipation, dyspepsia, abdominal pain, melena, hematemesis, hypertension and heart failure as well as ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported. Less frequently, gastritis was seen.

In the majority of cases where aseptic meningitis has been reported, there has been some form of underlying autoimmune disease (in particular, systemic lupus erythematosus and related connective tissue diseases).

Immune system disorders: Following therapy with NSAIDs, hypersensitivity reactions have been reported. These were consisting of non-specific allergic reactions and anaphylaxis, respiratory tract reactivity such as asthma, aggravated asthma, bronchospasm and dyspnea or skin disorders including rash (various types), pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiform).

Exceptionally, occurrence of serious skin and connective tissue infectious complications have been reported in connection with varicella

Ibuprofen can inhibit reversible platelet aggregation, resulting in prolongation of bleeding time.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose and treatment

Ibuprofen Toxicity
There is risk of symptoms occurring at doses above 80–100 mg/kg. At doses above 200 mg/kg there is a risk of severe symptoms, though with considerable variations between individuals. A dose of 560 mg/kg in a child aged 15 months resulted in severe intoxication, 3,2 g in a 6-year-old mild to moderate intoxication, 2,8–4 g in a 1½-year-old and 6 g in a 6-year-old severe intoxication, 8 g in an adult moderate intoxication and >20 g in an adult very severe intoxication. 8 g administered to a 16-year-old affected the kidney and 12 g in combination with alcohol administered to a teenager resulted in acute tubular necrosis.

Symptoms
The predominant symptoms are from the gastrointestinal tract, e.g. nausea, abdominal pains, vomiting (possibly blood-streaked) and headache, tinnitus, confusion and nystagmus. At high doses

loss of consciousness, convulsions (mainly in children). Bradycardia, fall in blood pressure. Hypernatremia, kidney effects, hematuria. Possibly liver effects. Hypothermia and adult respiratory distress syndrome has rarely been reported. Metabolic acidosis may occur in severe intoxications.

Treatment
If warranted, gastric lavage, carbon. In the event of gastrointestinal problems, antacids are administered. In the event of hypotension, intravenous fluid and, if required, inotropic support. Ensure adequate diuresis. Correction of acid-base and electrolyte disorders. Frequent and prolonged convulsions must be treated with intravenous diazepam. Administer other symptomatic therapy.

Chlorpheniramine maleate toxicity
If ingested at a dose level 3 to 5 times the daily recommended dose, it leads to intoxication. Children are more susceptible to the anticholinergic toxic effects of antihistamine drugs compared to adults. Symptoms and signs include sedation, paradoxical stimulation of the CNS, toxic psychosis, convulsions, apnea, anticholinergic effects, dystonic reactions, arrhythmias and cardiovascular collapse. The lethal dose of chlorpheniramine is 25mg to 50mg/kg.

If necessary, essential and advanced life support should be given. If there is ventricular fibrillation without pulse, defibrillation is implemented. Due to the anticholinergic effect, signs and symptoms of intoxication may delay, therefore patients without findings should be monitored for at least 6 to 8 hours. Hypotension and arrhythmias should aggressively be treated. Coma, convulsions, hypothermia and ventricular tachycardia should be expected during monitorization.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Cough and Cold Preparations
ATC Code: R05X

Mechanism of action:
Ibuprofen is a propionic acid derivative having analgesic anti-inflammatory and antipyretic effects. Therapeutic effects of ibuprofen are thought to occur as a result of its inhibitory effect on cyclooxygenase enzyme. Due to this inhibitory effect, ibuprofen leads to a significant decrease in prostaglandin synthesis.

Experimental data show that, when used concurrently, ibuprofen can competitively inhibit the effect of low-dose acetylsalicylic acid on platelet aggregation. In some pharmacodynamic studies, it was observed that the effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation was reduced when a single dose of 400 mg ibuprofen was taken within 8 hours prior to the immediate release acetylsalicylic acid dose (81 mg) or within 30 minutes after the dose. Although there is uncertainty about the clinical extrapolation of these data, the possibility that long-term and continuous use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. A clinically significant effect with occasional ibuprofen is unlikely to be observed (see section 4.5).

Chlorpheniramine maleate, which is an alkylamine derivative, is a potent antihistaminic. It also has anticholinergic activity. Due to its H1 receptor antagonist properties, it provides temporary relief of allergic symptoms such as runny nose, watery eyes and sneezing resulting from allergic conditions of upper respiratory tract. It is an antihistamine with good therapeutic effects. Antihistamines provide symptomatic relief, which lasts as long as the therapy continues.

5.2. Pharmacokinetic properties

General characteristics

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. Peak plasma concentrations are reduced and time to reach these levels is slower when ibuprofen is taken with food compared to when taken on an empty stomach. Food does not affect the total bioavailability to a relevant extent.

Chlorpheniramine maleate is well absorbed when taken orally. Its effect starts within 15 to 60 minutes, maximum effect is achieved within 3 to 6 hours.

Distribution:

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.

About 70% of chlorpheniramine is bound to plasma proteins. Chlorpheniramine is widely distributed in the body, including the central nervous system. It crosses the placenta and enters breast milk.

Biotransformation:

Ibuprofen is metabolized in the liver to two inactive metabolites.

The metabolism of chlorpheniramine is extensive and rapid, first occurring in the gastrointestinal mucosa and then on first-pass through the liver, N-dealkylation produces several metabolites.

Elimination:

Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

Chlorpheniramine is renally eliminated, mostly as metabolites within 24 hours. Renal elimination rate depends on the urine pH and urine flow; as the urine pH increases and urinary flow decreases, the elimination rate is slowed.

Linearity/Non-linearity:

The kinetic behavior of Ibuprofen and Chlorpheniramine is linear.

Characteristics in patients

Renal impairment:

For patients with mild renal impairment increased unbound (S)-ibuprofen, higher Area under the Curve (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 hemodialysis (see sections 4.2, 4.3 and 4.4).

Hepatic impairment:

Alcoholic liver disease with 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).

Elderly
In cases without renal insufficiency, in pharmacokinetic profile and urinary excretion, only minor, clinically insignificant changes are observed between young and elderly patients.

Children
The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg body weight) in children aged one 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.

5.3. Preclinical safety data

Acute toxicity(ibuprofen):

Species	Sex	Dosing range mg/kg	Max. Ineffective level mg/kg	Min. Dose with apparent effect mg/kg	Max. non-lethal dose mg/kg	Min. lethal dose mg/kg	Max. Non-fetal dose mg/kg
Mouse (oral)	M	200-1600	200	400	200	400	800
Mouse (ip)	M	100-1600	100	200	100	200	800
Rat (oral)	M	400-1600	400	800	800	1600	1600
Rat (sc)	M	400-1600	800	1600	800	1600	1600

Chronic toxicity (ibuprofen):
Gastrointestinal tract ulceration was the only constant pathological finding, which were seen with the following lowest daily doses: 300 mg/kg in mice; 180 mg/kg in rats; 100 mg/kg in monkeys; 8 mg/kg in dogs. No gastrointestinal damage level was 60 mg/kg a day for 6 months in rats and 75 mg/kg a day for 90 days in mice. In a study, renal papillary changes were found in rats at the end of two-years. These findings are typical for non-steroidal anti-inflammatory drugs and relevance of these to humans is in question.

Chlorpheniramine maleate:
Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Xanthan gum
Hydroxypropyl methyl cellulose
Glycerin
Sorbitol (70%) (E420)
Citric acid monohydrate
Sodium benzoate (E211)
Polyoxyl 40 castor oil
Sucrose
Strawberry flavor
Masking flavor
Ammonium glycyrrhizate
Microcrystalline cellulose and carboxymethylcellulose sodium (carmellose sodium)
Ponso 4R (E124)
Deionized water

6.2. Incompatibilities

There is no evidence for any existing incompatibilities of IBURAMIN ZERO with any drug or agent.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25ºC.

6.5. Nature and contents of container

IBURAMIN ZERO is marketed in amber colored glass bottles (Type III) closed with pilfer-proof high density polyethylene cap and low density polyethylene seal.

Each carton box contains 1 bottle and 1 spoon of 5 ml.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with “Directive on Control of Medical Waste” and “Directive on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

252/25

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24/07/2013
Date of latest renewal: 29/11/2018

10. DATE OF REVISION OF THE TEXT

02.05.2019