SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IBURAMIN COLD 200 mg/30 mg/2 mg FILM COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains;

Active substances:

Ibuprofen DC 90%(equivalent to 200 mg ibuprofen)	222 mg
Pseudoephedrine hydrochloride	30 mg
Chlorpheniramine maleate	2 mg

Excipients:

Lactose monohydrate (made from cow milk)	251.87 mg
The carmoisine (azorubin) aluminum lac (E122)	0.168 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.
Pink colored, oblong film coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for the relief of symptoms associated with common cold, flu, sinusitis and other upper respiratory tract infections such as fever, runny nose and nasal congestion.

4.2. Posology and method of administration

Posology/frequency of administration and duration:

For adults, elderly and people over 12 years of age, it should be used for maximum 5 days until the symptoms are relieved.

Each 4 or 6 hours, 1 or 2 film coated tablets can be used. And maximum 6 film coated tablets can be used within 24 hours.

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

Additional information on special populations:
Renal/hepatic impairment:

It should not be used in persons with hepatic and renal dysfunction.

Pediatric population
Not to be used for children under the age of 12.
Geriatric patients:
The risk of gastric bleeding due to ibuprofen increases in patients over 60 years of age.

4.3. Contraindications

IBURAMIN COLD is contraindicated in the following situations:

- Patients having hypersensitivity to the active substances or any of the excipients in the product or other adrenergic drugs
- Patients with severe hypertension and accompanying diseases of tachycardia
- Coronary arterial disease
- Patients under treatment with monoamino oxidase inhibitors (patients who have taken and/ or continue taking a MAO inhibitor (including an antibacterial agent, furazolidone) / the reversible MAO inhibitor (RIMA) within 14 days before administration of IBURAMIN COLD). Concurrent use of pseudoephedrine and such drugs may lead to an increase in blood pressure.
- Co-administration of it with the other sympathomimetic drugs (decongestants, appetite suppressing medications or amphetamine like psychostimulants) and beta-blocking agents
- Children under 12 years of age
- Last trimester of pregnancy
- Patients with severe hepatic failure
- Patients with increased bleeding tendency
- Patients who have previously developed hypersensitivity reactions (e.g. asthma, rhinitis, or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs (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 severe heart failure (NYHA Class IV)
- Patients in the period of pre or post-coronary artery bypass surgery.

4.4. Special warnings and precautions for use

Ibuprofen:

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

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

Gastrointestinal Risk
NSAIDs cause an increased risk of 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.

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).

IBURAMIN COLD 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.

IBURAMIN COLD 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 IBURAMIN COLD in patients with a history of heart failure or hypertension as oedema cases associated with ibuprofen therapy have been reported.

As with the other NSAIDs, IBURAMIN COLD may mask the symptoms of infection.

Cardiovascular and cerebrovascular effects
Hypertension and / or mild to moderate congestive heart failure patients with a history of proper monitoring and advising on their condition is necessary because in association with NSAID therapy, fluid retention and edema have been reported.

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 an NSAID 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 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.

Hypertension:
NSAIDs including IBURAMIN COLD, 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 IBURAMIN COLD, 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. IBURAMIN COLD should be used with caution in patients with fluid retention or heart failure.

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 and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including IBURAMIN COLD, 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 event 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 bleed 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, alternate 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 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.

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 precipitate overt renal decompensation. 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 Disease

No information is available from controlled clinical studies regarding the use of IBURAMIN COLD in patients with advanced renal disease. Therefore, treatment with IBURAMIN COLD is not recommended in these patients with advanced renal disease. If IBURAMIN COLD 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 IBURAMIN COLD previously. IBURAMIN COLD 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.

Haematological effects

In patients receiving NSAIDs including IBURAMIN COLD, 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 IBURAMIN COLD, hemoglobin and hemotocrit 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 IBURAMIN COLD 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, IBURAMIN COLD 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 erythematosus 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 IBURAMIN COLD should be avoided in case of the following conditions;

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

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

Pseudoephedrine:

Care should be taken for patients with

- Arrhythmias
- Cardiovascular disease
- Ischemic heart disease
- Diabetes mellitus
- Hyperthyroidism
- Glaucoma
- Renal impairment
- Thyroid function disorders
- Pheochromocytoma.
- Hypertension
- Although pseudoephedrine has virtually no pressor effects in normotensive patients, IBURAMIN COLD should be used with caution in individuals suffering from mild to moderate hypertension (See Section 4.3. Contraindications, Section 4.5 Interaction with other medicinal products and other forms of interaction). The effects of IBURAMIN COLD on blood pressure should be monitored in patients with uncontrolled hypertension.
- Care should be taken for patients with prostatic hypertrophy (hyperplasia) and those with bladder dysfunction
- It should be discontinued when hallucinations, restlessness, sleep disturbances occur.
- Care should be taken for those with severe hepatic impairment and renal impairment, in particular those with accompanying cardiovascular disease.
- Care should be taken for patients over 60 years of age
- There have been rare cases of posterior reversible encephalopathy (PRES)/reversible cerebral vasoconstriction syndrome (RCVS) reported with sympathomimetic drugs, including pseudoephedrine. Symptoms reported included sudden onset of severe headache, nausea, vomiting, and visual disturbances. Most cases improved or resolved within a few days following appropriate treatment. Pseudoephedrine should be discontinued immediately and medical advice sought if any signs/symptoms of PRES/RCVS develop.

- It should not be used for more than 5 days.

This drug should be avoided for use in patients with diagnosed or suspected congenital prolonged QT syndrome or Torsades de Pointes.

Chlorpheniramine maleate:

This drug should be avoided for use in patients with the following conditions:

- Epilepsy
- Prostatic hypertrophy
- Glaucoma
- Bronchitis, bronchiectasis, asthma
- Hypertension
- Cardiovascular disease
- Hyperactive thyroid function disorders

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

Due to its lactose monohydrate content, this medicinal product should not be used in patient with rare hereditary, galactose intolerance, Lapp lactase deficiency or glucose -galactose malabsorption**.**

It may cause allergic reactions due to the coloring agent carmoisine (azorubin) aluminum lac (E122) in its content.

4.5. Interaction with other medicinal products and other forms of interaction

Ibuprofen:

Combined use of IBURAMIN COLD 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 additive 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 potential for increased adverse effects. Experimental data suggests that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when used simultaneously. 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 can not be ruled out. A clinically significant effect with ibuprofen, which is used intermittently, is probably not expected (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 non-steroidal anti-inflammatory drugs (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.

<u>Concomitant use of ibuprofen with the following agents may require dose adjustment:</u>

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 can not 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).

Cyclosporin: It is presumed that administering of NSAIDs concomitantly with cyclosporin 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.

Pseudoephedrine:

IBURAMIN COLD should not be used in patients taking MAOI/RIMA.Concomitant use of it with tricyclic antidepressants, appetite suppressants, sympathomimetic agents (such as

decongestants, appetite suppressants and amphetamine-like psychostimulants) or with monoamine oxidase inhibitors (including furazolidone), which interfere with the catabolism of sympathomimetic amines, may occasionally cause a rise in blood pressure. (see. 4.3 Contraindications) Concomitant use with moclobemide and oxytocin may cause an increase in blood pressure. Because of its pseudoephedrine content, IBURAMIN COLD may partially reverse the hypotensive action of drugs which interfere with sympathetic activity including bretylium, bethanidine, guanethidine, debrisoquine, methyldopa, alpha- and beta-adrenergic blocking agents (see. 4.4 Special warnings and precautions for use). Cardiac glycosides may cause risk of dysrhythmia, ergot alkaloids may cause risk of ergotism.

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.

4.6. Pregnancy and lactation

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

Women with Childbearing Potential/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 available for Pseudoephedrine.

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, IBURAMIN COLD should not be given unless clearly necessary. If IBURAMIN COLD 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:

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

Consequently, IBURAMIN COLD is contraindicated during the third trimester of pregnancy.

Lactation

In limited studies, ibuprofen appears in the breast milk in very low concentrations and is unlikely to affect the breast-fed infant adversely. However, it is not recommended to use ibuprofen in lactating women.

Pseudoephedrine is secreted in breast milk in small amounts, but its degree of impact on breastfed babies remains unknown. It has been estimated that 0.5% to 0.7% of a single dose of pseudoephedrine ingested by the mother will be excreted in the breast milk over 24 hours. Therefore IBURAMIN COLD should be used with caution only for breastfeeding mothers when the doctor thinks that its potential benefits to the patient justify its possible risks to the infant.

Chlorpheniramine maleate is excreted in the breast milk in significant amounts; at these levels it is not known if it is harmful to babies, however its use is not recommended during lactation. Chlorpheniramine maleate and other antihistamines may inhibit lactation.

Fertility

In particular, concerning pseudoephedrine, since there is no information about the impact on fertility, decision to use pseudoephedrine should be made by the physician, considering benefit / risk ratio.

The use of ibuprofen may impair female 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 and 25 times the maximum recommended human dose on a mg/m2 basis, respectively.

4.7. Effects on ability to drive and use machines

IBURAMIN COLD 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 from available data).

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

Blood and lymphatic system disorders
Rare: Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and hemolytic anemia.
Not known: Blood dyscrasias

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

Psychiatric disorders
Common: Nervousness, insomnia
Uncommon: Fatigue, frustration, agitation (restlessness)
Rare: Hallucinations (particularly in children), paranoid delusions, restlessness, excitability

Nervous system disorders
Common: Drowsiness, headache, dizziness
Uncommon: Paresthesia
Rare: Optic neuritis, somnolence
Not known: Irritability, anxiety

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

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

Cardiac disorders
Rare: Tachycardia, other cardiac dysrhythmias
Very rare: Arterial thrombotic events (ibuprofen intake at higher dose e.g. 2400 mg/ daily)

Vascular disorders
Rare: Blood pressure increased*
* Increases in systolic blood pressure have been observed. At therapeutic doses, the effects of pseudoephedrine on blood pressure are not clinically significant.

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
Rare: Gastrointestinal perforation, 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

Metabolism and nutritional disorders:
Not known: Loss of appetite

Skin and subcutaneous tissue disorders
Common: Skin rash
Uncommon: Urticaria, pruritus, purpura, angioedema, photosensitivity
Rare: Skin rashes with or without irritations, hypersensitivity reactions, cross-reactivity to the other sympathomimetics, allergic dermatitis*
Very rare: bullous skin inflammation including Stevens-Johnson's syndrome, toxic epidermal necrolysis and erythema multiforme.
Not known: Exfoliative dermatitis

*A variety of allergic skin reactions, with or without systemic features such as bronchospasm and angioedema have been reported following use of pseudoephedrine.

Renal and urinary disorder
Uncommon: Dysuria, urinary retention in male patients (pre-existing prostatic hyperplasia may be a preliminary factor), tubule interstitial nephritis, nephrotic syndrome and renal impairment.

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

Edema, hypertension and heart failure have been reported in association with non-steroidal anti-inflammatory therapy. Clinical trials have shown that the use of ibuprofen, especially 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) (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 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, eg 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 multiforme).

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

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

4.9 Overdose

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. Metabolic acidosis, hypernatremia, kidney effects, hematuria. Possibly liver effects. Hypothermia. Adult respiratory distress syndrome (ARDS) has occasionally been reported.

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. Frequent and prolonged convulsions must be treated with intravenous diazepam. Correction of acid-base and electrolyte disorders. Other symptomatic therapy.

Pseudoephedrine toxicity

Symptoms
In addition to its adverse effects seen with the recommended doses, in case of acute overdose tremor, convulsions, irritability, restlessness, palpitations, hypertension may be seen.

Treatment

Necessary measures should be taken to maintain and support respiration and control convulsions. Gastric lavage may be undertaken if indicated. Catheterization of the bladder may be necessary. Acid diuresis can accelerate the elimination of pseudoephedrine although the potential therapeutic gain of this procedure is now in dispute. The value of dialysis in overdose is not known, although four hours of hemodialysis removed approximately 20% of the total body load of pseudoephedrine in an instant-release combination product containing 60 mg pseudoephedrine and 8 mg acrivastine.

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 estimated lethal dose of chlorpheniramine is 25mg to 50mg/kg body weight.

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

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 non-selective inhibitory effect on cyclooxygenase isoenzymes (COX-1 and COX-2). Due to this inhibitory effect, ibuprofen leads to a significant decrease in prostaglandin synthesis.

Experimental data shown that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when used simultaneously. In some pharmacodynamic studies, the efficacy of acetylsalicylic acid in 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 fast-acting 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 can not be ruled out. A clinically significant effect with ibuprofen, which is used intermittently, is probably not expected (see Section 4.5).

Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory decongestant. Pseudoephedrine is less potent than ephedrine in producing both elevation of systolic blood pressure and tachycardia and is also less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes of dosing, persisting for up to 4 hours. Pseudoephedrine 60 mg has been shown to be an effective nasal decongestant, as measured by nasal airflow, in patients with the common cold and

rhinitis and normal individuals and patients with allergic rhinitis following histamine administration.

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 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. 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.

Pseudoephedrine is rapidly and completely absorbed from the gastrointestinal tract after oral administration, with no presystemic metabolism. Administration of 60 mg pseudoephedrine to healthy volunteers, provided approximately 180 ng/ml of peak plasma concentration (Cmax) with Tmax approximately 1.5 hours after drug administration.

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.

The apparent volume of distribution (Vd/F) for Pseudoephedrine is 2.81 l/kg.

About 70% of chlorpheniramine in the circulation 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 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.

The plasma half-life (t½) was approximately 5.5 hours. Pseudoephedrine is metabolized to only a minor extent in men, approximately 90% of a dose is excreted unchanged. Approximately 1% of a dose is metabolized by the liver, by N-demethylation to norpseudoephedrine.

The metabolism of chlorpheniramine is extensive and rapid, first occurring in the gastric

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.

Pseudoephedrine and its metabolite are excreted in the urine; 55% to 90% of a dose is excreted unchanged. The apparent total body clearance of pseudoephedrine (Cl/F) was 7.5 mL/min/kg. The elimination rate constant (Kcl) was approximately 0.13 hr-1. The rate of urinary elimination is accelerated when the urine is acidified. Conversely, as the urine pH increases, the rate of urinary excretion is slowed. Renal impairment will result in increased plasma levels of pseudoephedrine. As a weak base, the extent of renal excretion is dependent on urinary pH. At low urinary pH, tubular resorption is minimal and urine flow rate will not influence clearance of the drug. At high pH (>7.0), pseudoephedrine is extensively reabsorbed in the renal tubule and renal clearance will depend on urine flow rate.

Chlorpheniramine is renally eliminated, mostly as metabolites within 24 hours.
Linearity/Non-linearity
The kinetic behavior of Ibuprofen, Pseudoephedrine 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).

Renal impairment leads to increased plasma levels of Pseudoephedrine. There have been no specific studies of IBURAMIN COLD in renal impairment. Following the administration of a single dose of 8 mg acrivastine + 60 mg pseudoephedrine capsules to patients with varying degrees of renal impairment, the Cmax for pseudoephedrine increased approximately 1.5 fold in patients with moderate to severe renal impairment when compared to the Cmax in healthy volunteers. The tmax was not affected by renal impairment. The half life increased 3 -12 fold in patients with mild to severe renal impairment respectively, when compared to the half life in healthy volunteers.

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 unsignificant changes are observed between young and elderly patients.

After the administration of 60 mg pseudoephedrine + 8 mg acrivastine to elderly volunteers, the t½ for pseudoephedrine was 1.4 fold that seen in younger healthy volunteers. The apparent Cl/F was 0.8 fold that seen in younger healthy volunteers, and the Vd/F was unchanged. There have been no specific studies of IBURAMIN COLD in the elderly.

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

Ibuprofen:
Acute toxicity:

Species	Sex	Dosing range mg/kg	Max. Ineffective level mg/kg	Min. Dose with apparent effect	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:
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.

Pseudoephedrine:
Mutagenicity: Pseudoephedrine was not genotoxic in bacterial and mammalian *in vivo* and *in vitro* tests.
Carcinogenicity: There is insufficient information available to determine whether pseudoephedrine has carcinogenic potential.
Teratogenicity:
Systemic administration of pseudoephedrine up to 432 mg/kg/day in rats and up to 200 mg/kg/day in rabbits did not produce teratogenic effects.

Chlorpheniramine maleate:

Not applicable.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Lactose monohydrate (made from cow milk)
Microcrystalline cellulose pH102
Povidone K30
Magnesium stearate
Croscarmellose sodium
Colloidal silicon dioxide
Hypromellose
Polyethylene glycol
Titanium dioxide (E171)
Carmoisine (azorubin) aluminium lac (E122).

6.2. Incompatibilities

There is no evidence for any existing incompatibilities of IBURAMİN COLD 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 COLD are marketed in PVC/PVDC/Aluminum blisters as 12 and 24 tablets.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 26.12.2013
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

07.06.2018