SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DROFLU COLD 200mg/30 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Ibuprofen	200 mg
Pseudoephedrine hydrochloride	30 mg

Excipients:

Croscarmellose sodium	34 mg

See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet

4. CLINICAL PROPERTIES

4.1. Therapeutic indications

DROFLU COLD is used to relieve nasal congestion, headache, fever, body aches and other pains seen in the course of diseases such as flu, colds or sinusitis.

4.2. Posology and method of administration

Posology/administration frequency and duration:

In adults and children over 12 years of age, the recommended starting dose should be 2 tablets, followed by 1-2 tablets every 4 hours if necessary.

Unless recommended by the physician, it should not be taken more than 6 tablets per day. The smallest effective dose should always be used.

It is for short term use.

It should not be used for longer than 5 days.

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

Method of administration:

DROFLU COLD is for oral use only.

Tablets should be taken as a whole, without breaking or chewing, with 1 glass of water.

Additional information on special populations:

Kidney/Liver failure:

The use of DROFLU COLD should be avoided in patients with severe hepatic impairment.

It should be used with caution in moderate renal failure. It should not be used in severe renal failure.

Pediatric population:

It should be used in children 12 years and older.

Geriatric population:

The frequency of undesirable effects such as gastrointestinal bleeding and perforation, which can be fatal, increases with the use of NSAIDs in this patient group.

It should be used with caution in patients over 60 years of age, with hypertension, hyperthyroidism, diabetes mellitus, cardiovascular disease, ischemic heart disease, glaucoma or prostatic hypertrophy (hyperplasia). Long-term use should be avoided.

4.3. Contraindications

DROFLU COLD should not be used in patients with hypersensitivity to ibuprofen or pseudoephedrine, other adrenergic drugs, or any of the excipients in the drug.

DROFLU COLD is contraindicated in patients who have previously developed a hypersensitivity reaction such as asthma, rhinitis, urticaria with ibuprofen, aspirin or other NSAIDs. In such patients, it may cause severe, rarely fatal, anaphylaxis-like reactions.

DROFLU COLD is contraindicated in patients with active gastric and duodenal ulcers. It is contraindicated in patients with a history of gastrointestinal bleeding or perforation associated with previous NSAIDs.

DROFLU COLD is contraindicated in the third trimester of pregnancy.

The use of DROFLU COLD as a preoperative pain reliever is contraindicated in patients undergoing coronary artery by-pass graft operation.

DROFLU COLD is contraindicated in patients with cerebrovascular bleeding or any active bleeding.

DROFLU COLD is contraindicated in coronary artery disease, in diseases accompanied by severe hypertension and tachycardia.

Concomitant use of DROFLU COLD with monoaminooxidase inhibitors, tricyclic antidepressants, other sympathomimetic drugs (decongestants, appetite suppressants or amphetamine-like psychostimulants) and beta-blockers is contraindicated.

DROFLU COLD is also contraindicated in severe heart failure (NYHA Class IV), severe hepatic impairment and severe renal impairment.

DROFLU COLD is contraindicated in children under 12 years of age.

DROFLU COLD is contraindicated in patients with diabetes mellitus, hyperthyroidism, glaucoma, and pheochromocytoma.

4.4. Special warnings and precautions for use

Cardiovascular (CV) risks

- NSAIDs may increase the risk of potentially fatal CV thrombotic events, myocardial infarction, and stroke. This risk may increase depending on the duration of use. The risk may be higher in patients with CV disease or those with CV disease risk factors.

- DROFLU COLD is contraindicated in the treatment of pain before coronary artery bypass surgery.

Gastrointestinal (GI) risks

- NSAIDs cause serious GI adverse effects such as bleeding, ulceration, perforation of the stomach or intestines, which can be fatal. These adverse events can occur at any time, with or without a forewarning symptom.

- Elderly patients are at higher risk for serious GI effects.

Because of the cumulative risk of triggering serious adverse events associated with NSAIDs, concomitant administration of DROFLU COLD and other NSAIDs is not recommended.

Hypersensitivity reactions to NSAIDs often occur in individuals with pre-existing asthma or allergic diseases. DROFLU COLD should be used with caution in this group of patients.

There is some evidence that drugs that inhibit cyclooxygenase/prostaglandin synthesis may have effects on fertility by affecting ovulation. After discontinuation of treatment, the previous state is restored.

Ibuprofen
DROFLU COLD is not to be used in place of corticosteroids or for the treatment of corticosteroid insufficiency. Sudden discontinuation of corticosteroids may lead to exacerbation of the disease. If corticosteroid therapy is to be discontinued in patients receiving long-term corticosteroid therapy, treatment should be tapered slowly.

The pharmacological activity of DROFLU COLD for the reduction of fever and inflammation may reduce the usability of diagnostic findings to identify complications that are predicted to be non-infectious, painful.

Cardiovascular effects
Cardiovascular thrombotic events
Clinical trials of various COX-2 selective and non-selective NSAIDs lasting up to three years have demonstrated an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All COX-2 selective or non-selective NSAIDs may have similar risks. Patients with known CV disease or CV risk factors are at greater risk. To minimize the potential CV risk in patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should be prepared for such symptoms even if they do not have previous CV symptoms. Patients should be informed about serious CV signs and/or signs and what to do if they occur.

There is no consistent evidence that concomitant use of aspirin reduces the increased risk of serious CV thrombotic events associated with NSAID use. Concomitant use of aspirin and NSAIDs increases the risk of serious gastrointestinal (GI) events (see Gastrointestinal effects – risk of ulceration, bleeding and perforation).

An increased incidence of myocardial infarction and stroke has been found in two large, controlled clinical trials of COX-2 selective NSAIDs for the treatment of pain in the first 10-14 days after CABG surgery (see Section 4.3 Contraindications).

Clinical studies indicate that the use of ibuprofen, particularly at high doses (2400 mg/day), may be associated with a small increased 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.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), pre-existing ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease should be treated with ibuprofen only after careful consideration and avoiding high doses (2400 mg/day). . Careful consideration should also be given before initiating long-term therapy in patients with risk factors for cardiovascular events (eg hypertension, hyperlipidemia, diabetes, smoking), especially when high doses of ibuprofen (2400 mg/day) are required.

Hypertension

NSAIDs, including DROFLU COLD, cause the development of new hypertension or worsening of existing hypertension, and each of these disorders may contribute to an increased risk of CV events. In patients taking thiazide or loop diuretics while taking NSAIDs, the response to these therapeutics may be impaired. NSAIDs, including DROFLU COLD, should be used with caution in patients with hypertension. Blood pressure (BP) should be closely monitored during initiation and throughout treatment with NSAIDs.

Congestive heart failure and edema

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

Gastrointestinal effects – risk of ulceration, bleeding and perforation

NSAIDs, including DROFLU COLD, can cause serious gastrointestinal (GI) adverse events such as inflammation, bleeding, ulceration, perforation of the stomach, small and large intestines, which can be fatal. These serious adverse events can occur at any time in patients treated with NSAIDs, with or without warning symptoms. Only one in five patients who develop a serious upper GI adverse event during NSAID therapy is symptomatic. Upper GI tract ulcers, heavy bleeding, and perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months and in approximately 2-4% of patients treated for 1 year. This trend persists with long-term use and increases the likelihood of serious GI events at any time during treatment. But even short-term treatment is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a history of prior ulceration or gastrointestinal bleeding. Patients with a prior history of peptic ulcer and/or gastrointestinal bleeding and taking NSAIDs have a 10-fold increased risk of GI bleeding compared to patients without these risk factors.

Other factors that increase the risk of GI bleeding in patients treated with NSAIDs are concomitant use of oral corticosteroids or anti-coagulants, long-term use of NSAIDs, smoking, alcohol use, advanced age, and poor general condition. Most spontaneous reports of fatal GI events are in elderly or poor general health patients, so caution should be exercised in the management of these patient groups.

To minimize the potential risk of GI events in patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible time. Physicians and patients should be prepared for the signs and symptoms of GI bleeding and ulceration that may develop during NSAID use, and additional evaluation and treatment should be initiated promptly if they suspect a serious GI adverse event. This approach should be discontinuation of NSAIDs until the resolution of the serious GI adverse event. Alternative treatments without NSAIDs should be considered for high-risk patients.

Renal effects

Long-term use of NSAIDs causes renal papillary necrosis and other kidney damage. Renal toxicity has also been observed in patients with a compensatory effect of prostaglandins in maintaining renal perfusion. The use of non-steroidal anti-inflammatory drugs in these

patients may cause a dose-dependent decrease in the production of prostaglandins and, secondarily, a clear acceleration of renal decompensation by reducing renal blood flow.

The risk of this reaction is higher in patients with renal dysfunction, heart failure, hepatic failure, those taking diuretics and ACE inhibitors, and the elderly. With the discontinuation of NSAID therapy, the pre-treatment state is usually restored.

Advanced kidney disease

There are no controlled clinical trial data on the use of ibuprofen in patients with advanced kidney disease. Therefore, DROFLU COLD is not recommended in patients with advanced kidney disease. If DROFLU COLD is to be used, close follow-up of patients' kidney functions is appropriate.

Anaphylactoid reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients with unknown prior exposure to DROFLU COLD. DROFLU COLD should not be given to patients with the aspirin triad. This symptom complex typically develops in patients with asthma with or without nasal polyps, rhinitis, or patients who exhibit severe bronchospasm, potentially fatal, after taking aspirin or other NSAIDs (see Section 4.4 Special warnings and precautions for use - Pre-existing asthma). Emergency intervention should be considered in cases of anaphylactoid reaction.

Ocular effects

Studies have not demonstrated ocular changes attributable to ibuprofen administration. In rare cases, undesirable ocular disorders such as papillitis, retrobulbar optic neuritis, and papilledema have been reported by users of NSAIDs, including ibuprofen; however, a causal and effect relationship has not been established; therefore, patients who develop visual impairment during ibuprofen treatment should undergo an ophthalmologic examination.

Skin reactions

NSAIDs, including DROFLU COLD, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), which can be fatal. These serious events can occur without warning. Patients should be alerted

to the signs and symptoms of serious skin conditions, and drug use should be discontinued when skin rash or other signs of hypersensitivity occur.

Pregnancy

As with other NSAIDs in the last period of pregnancy, ibuprofen should be avoided as it may cause premature closure of the ductus arteriosus.

Hepatic effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including DROFLU COLD. These laboratory abnormalities may progress, persist, or be transient over the course of treatment. Significant elevations of ALT and AST (three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials of NSAIDs. Rarely, serious hepatic reactions including jaundice and fatal fulminant hepatitis, hepatic necrosis and hepatic failure (some with fatal outcome) have been reported.

Evidence of the development of more serious liver reactions should be investigated when a patient develops signs and/or signs of liver dysfunction during treatment with DROFLU COLD, or in those with abnormal liver tests. If clinical signs or symptoms associated with liver disease or systemic manifestations (eg, eosinophilia, skin rash, etc.) occur, DROFLU COLD treatment should be discontinued.

Hematological effects

Anemia may occasionally be observed in patients taking NSAIDs, including DROFLU COLD. This is due to fluid retention, latent or overt GI blood loss, or incompletely defined effects on erythropoiesis. In patients taking long-term NSAIDs, including DROFLU COLD, hemoglobin and hematocrit values should be checked if any signs or symptoms of anemia are observed.

NSAIDs have been shown to inhibit platelet aggregation and prolong bleeding time in some patients. Unlike aspirin, its effects on platelet functions are quantitatively less, short-lived, and reversible. Patients receiving DROFLU COLD who are adversely affected by changes in platelet function, as well as patients with coagulation disorders or taking anti-coagulants, should be carefully monitored.

Pre-existing asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, DROFLU COLD should not be administered to these patients and should be used with caution in patients with pre-existing asthma.

Patients should be informed about the following points before starting the treatment and during the treatment.

- Like other NSAIDs, ibuprofen can cause serious CV side effects, such as myocardial infarction or stroke, which may result in hospitalization or even death. Although serious CV side effects can occur without any warning symptoms, patients should be alert for symptoms and signs such as chest pain, shortness of breath, weakness, and speech impairment and should consult their physician when observing any symptom or sign indicative of the disease. Patients should be informed of the importance of this monitoring (see Section 4.4 Special warnings and precautions for use – Cardiovascular effects).
- Like other NSAIDs, ibuprofen can cause serious GI side effects such as ulcers and bleeding, which can lead to GI discomfort and, rarely, hospitalization and even death. Although severe GI tract ulceration and bleeding can occur without warning symptoms, patients should be alert for the symptoms and signs of ulceration and bleeding and should consult their physician whenever they observe any symptom or sign indicative of the disease, such as epigastric pain, dyspepsia, melena, and hematemesis. Patients should be informed of the importance of this monitoring (see Section 4.4 Special warnings and precautions for use – Gastrointestinal effects – Risk of ulceration, bleeding and perforation).
- Like other NSAIDs, ibuprofen can cause serious dermatological side effects such as exfoliative dermatitis, SJS, and TEN, which can lead to hospitalization and even death. Although serious skin reactions can occur without warning, patients should be alert for signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity, such as pruritus, and should consult their physician when observing any indicative symptoms or signs. If any rash develops, patients should be advised to discontinue the drug immediately and consult their physician as soon as possible.

- Patients should promptly report any signs or symptoms of unexplained weight gain or edema to their physician.
- Patients should be informed of the signs and symptoms of hepatotoxicity (nausea, fatigue, lethargy, jaundice, right upper quadrant tenderness and cold-like symptoms). If these occur, patients should discontinue treatment and seek prompt medical treatment.
- Patients should be informed of the signs of an anaphylactic reaction (difficulty in breathing, swelling of the face and throat). When these occur, patients should be warned to rush to the emergency room (see Section 4.4 Special warnings and precautions for use).
- Like other NSAIDs, ibuprofen should not be taken in late pregnancy because it may cause premature closure of the ductus arteriosus.

Laboratory tests

Physicians should closely monitor for signs and symptoms of GI bleeding, as severe GI tract ulceration and bleeding can occur without any warning symptoms. Complete blood count and chemical profile should be monitored regularly in patients on long-term treatment with NSAIDs. Ibuprofen treatment should be discontinued if clinical symptoms and signs consistent with liver or kidney disease develop, if systemic manifestations occur (eosinophilia, rash, etc.), or if abnormal liver tests persist or worsen

Pseudoephedrine

It should be used with caution in the following situations:

- Aritmisi olanlarda
- Kardiyovasküler hastalığı olanlarda
- İskemik kalp hastalığı olanlarda
- Hafif-orta şiddette hipertansiyonu olanlarda

In normotensive patients, although pseudoephedrine has no apparent pressor effect, DROFLU COLD should be used with caution in patients with mild to moderate hypertension (see Contraindications, Interactions with other medicinal products and other forms of interaction). The effect of DROFLU COLD on blood pressure should be observed in patients with uncontrolled hypertension.

- Those with prostate hypertrophy (hyperplasia) and bladder dysfunction
- It should be discontinued when hallucinations, restlessness, sleep disturbance occur.
- Severe hepatic and renal impairment, especially those with concomitant cardiovascular disease
- Patients over 60 years of age

Posterior reversible encephalopathy (PRES)/reversible cerebral vasoconstriction syndrome (RCVS) has been reported infrequently with sympathomimetic drugs, including pseudoephedrine. Reported symptoms are sudden onset of severe headache, nausea, vomiting, and visual disturbances. Most cases resolved within a few days with appropriate treatment. Pseudoephedrine should be discontinued immediately if signs and symptoms of PRES/RCVS develop.

Long-term use should be avoided.
Its use should be avoided in patients with diagnosed and suspected congenital prolonged QT syndrome or Torsades de Pointes.

Pediatric population:
Not recommended for children under 12 years of age.

Geriatric population:
Since DROFLU COLD contains pseudoephedrine, it should not be used in patients over 60 years of age.
Since the elimination of the drug may be reduced in the elderly, care should be taken in dosage and the lowest effective dose should be applied.

Kidney/Liver failure:
As with other non-steroidal anti-inflammatory drugs, DROFLU COLD also has renal and hepatic dysfunction; It should be used with caution in people who have had kidney and liver disease in the past.

It has been reported that one or more of the liver function tests are impaired by the use of nonsteroidal anti-inflammatory drugs.

The use of DROFLU COLD should be avoided in patients with severe hepatic impairment.

It should be used with caution in moderate renal failure. It should not be used in severe renal failure.

This product contains 1 mmol (23 mg) sodium in each dose. This should be considered for patients on a controlled sodium diet.

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

Ibuprofen

Aminoglycosides

NSAIDs can reduce the excretion of aminoglycosides.

ACE inhibitors

It has been reported that NSAIDs can reduce the antihypertensive efficacy of ACE inhibitors. This interaction should be considered in patients taking ACE inhibitors with NSAIDs.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic. Therefore, those who use these drugs together have a higher risk of serious GI bleeding than those who use them separately.

SSRIs

The risk of gastrointestinal bleeding increases when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

Acetylsalicylic acid

Co-administration of acetylsalicylic acid and ibuprofen is not recommended due to the potential for increased adverse effects.

Experimental data indicate that, when used concomitantly, ibuprofen can competitively inhibit the effect of low-dose acetylsalicylic acid on platelet aggregation. Although there are uncertainties regarding the clinical extrapolation of these data, the possibility that prolonged and continued use of ibuprofen may reduce the cardioprotective effect of low-dose

acetylsalicylic acid cannot be excluded. A clinically significant effect is unlikely to be expected with occasional use of ibuprofen (see section 5.1).

Diuretics

Clinical studies and post-marketing observations have shown that DROFLU COLD reduces the natriuretic effect of some diuretics such as furosemide and thiazide. This effect has been associated with inhibition of renal prostaglandin synthesis. During concomitant treatment with NSAIDs, patients should be carefully monitored for signs of renal impairment and ensure continued diuretic efficacy.

Cardiac glycosides

NSAIDs can exacerbate cardiac failure, decrease glomerular filtration rate, and increase cardiac glycoside levels in plasma.

Quinolones

Data from animal studies have shown that NSAIDs may increase the risk of convulsions associated with quinolone antibiotics. Patients using quinolones may be at increased risk of developing convulsions.

COX-2 inhibitors and other NSAIDs

Due to potential additive effects, concomitant use with other NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.

Cholestyramine

Co-administration of ibuprofen with cholestyramine may reduce the absorption of ibuprofen from the gastrointestinal tract. But its clinical significance is unknown.

Corticosteroids

As with other NSAIDs, caution should be exercised when co-administered with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding.

If steroid dosage is to be reduced or discontinued during treatment, the steroid dosage should be reduced slowly and patients should be observed closely for adverse effects such as adrenal insufficiency and exacerbation of arthritis symptoms.

Lithium

NSAIDs caused an increase in plasma lithium levels and a decrease in renal lithium clearance. The mean minimum lithium concentration was increased by 15% and renal clearance was decreased by approximately 20%. These effects have been associated with inhibition of renal prostaglandin synthesis by NSAIDs. Therefore, when NSAIDs and lithium are used together, patients should be carefully monitored for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney sections. This may indicate that NSAIDs may increase methotrexate toxicity. Caution should be exercised when methotrexate and NSAIDs are used together.

Mifepristone

NSAIDs should not be used for 8-12 days after mifepristone administration, as NSAIDs may reduce the effect of mifepristone.

Cyclosporine

As with all NSAIDs, caution is required when used with cyclosporine due to the increased risk of nephrotoxicity.

Sulfonylurea

NSAIDs can potentiate sulfonylurea treatments. Very rare reports of hypoglycaemia have been reported with the use of ibuprofen in patients on sulfonylurea therapy.

Tacrolimus

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine

The risk of haematological toxicity may be increased when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthrosis and hematoma in HIV (+) hemophilia patients receiving concomitant therapy with zidovudine and ibuprofen.

CYP2C9 inhibitors

Co-administration of ibuprofen with CYP2C9 inhibitors may increase exposure to ibuprofen (CYP2C9 substrate). A study with voriconazole and fluconazole (CYP2C9 inhibitors) showed an increased S(+)-ibuprofen exposure of approximately 80-100%. Dose reduction of ibuprofen should be considered, particularly when high doses of ibuprofen are co-administered with potent CYP2C9 inhibitors such as voriconazole or fluconazole.

Herbal extracts

Ginkgo biloba may potentiate the risk of bleeding associated with NSAID use.

Pseudoephedrine

DROFLU COLD should not be used in MAOI/RIMA areas. Concomitant use with tricyclic antidepressants, appetite suppressants, sympathomimetic agents (such as decongestants, appetite suppressants, and amphetamine-like psychostimulants) and monoamine oxidase inhibitors (including furazolidone) that affect the catabolism of sympathomimetic amines can sometimes lead to increased blood pressure (see Contraindications). Concomitant use with moclobemide and oxytocin may cause hypertension. Because it contains pseudoephedrine, DROFLU COLD partially reverses the effect of hypotensive drugs that inhibit sympathetic activity, such as bretylium, betanidine, guanethidine debrizoquine, methyldopa and alpha and beta adrenergic blocking drugs (see Special warnings and precautions for use). Cardiac glycosides may cause dysrhythmia risk, and ergot alkaloids (ergotamine and methysergide) may cause ergotism risk.

Additional information on special populations:

No data available.

Pediatric population:

No data available.

4.6. Pregnancy and lactation

General advice

Pregnancy category: 1st and 2nd trimester: C; 3rd trimester: D

Women of childbearing potential/Contraception

It should not be used in women planning to become pregnant.

Pregnancy period

Animal studies are inconclusive regarding effects on pregnancy and/or embryonal/foetal development and/or parturition and/or postnatal development. The potential risk for humans is unknown. DROFLU COLD should not be used in the first 6 months of pregnancy unless necessary.

Ibuprofen is contraindicated in the third trimester because of the risk of premature closure of the fetal ductus arteriosus with possible permanent pulmonary hypertension. The onset of labor may be delayed and the duration of labor prolonged with increased bleeding tendency in mother and child (see section 4.3).

Lactation period

Pseudoephedrine is excreted in significant amounts, although ibuprofen is known to pass into breast milk at very low concentrations.

The use of DROFLU COLD should be avoided during the lactation period.

Reproductive ability/Fertility

There is some evidence that drugs that inhibit cyclooxygenase/prostaglandin synthesis may have effects on fertility by affecting ovulation. After discontinuation of NSAID therapy, the pre-treatment state is restored.

Orally administered pseudoephedrine at a dose of 20 mg/kg/day in female rats and 100 mg/kg/day in male rats did not impair reproduction or alter morphological development or life.

4.7. Effects on the ability to drive and use machines

Patients should be instructed not to drive or use machines, as dizziness may be observed.

4.8. Undesirable effects

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); unknown (cannot be estimated from the available data)

Blood and lymphatic system diseases

Very rare: Agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leukopenia and thrombocytopenia, pancytopenia (initial signs are fever, sore throat, superficial mouth ulcer, flu-like symptoms, severe malaise, bleeding from the nose and skin).

Immune system diseases

Uncommon: Hypersensitivity, urticaria, pruritus

Very rare: Signs of aseptic meningitis such as nuchal rigidity, headache, nausea, vomiting, fever or disorientation have been observed in patients with autoimmune disease (systemic lupus erythematosus, mixed connective tissue disease). Symptoms of severe hypersensitivity reactions (anaphylaxis, angioedema or severe shock) may include swelling of the face, tongue and throat, dyspnea, tachycardia, hypotension. Exacerbation of asthma and bronchospasm

Psychiatric diseases

Common: nervousness, insomnia

Uncommon: Fatigue, irritability, agitation (restlessness)

Rare: Hallucination (especially in children), paranoid delusion, excitability

Nervous system diseases

Common: Dizziness, drowsiness

Uncommon: Headache.

Very rare: Aseptic meningitis

Not known: Irritability, anxiety

Eye diseases

Very rare: Visual impairment.

Ear and inner ear diseases

Very rare: Tinnitus, vertigo

Cardiac diseases

Uncommon: Edema

Rare: Heart failure, tachycardia, palpitations, angina pectoris, other cardiac dysrhythmias

Vascular diseases

Rare: increased blood pressure

Respiratory, thoracic and mediastinal disorders

Very rare: Asthma, bronchospasm, dyspnoea, wheezing.

Gastrointestinal system diseases

Common: dry mouth, nausea, vomiting

Uncommon: Abdominal pain, dyspepsia, distention

Rare: Diarrhoea, flatulence, constipation

Very rare: GI ulcer (gastric/duodenal), GI perforation, exacerbation of ulcerative colitis or Crohn's disease, hematemesis, mouth ulceration

Hepato-biliary diseases

Very rare: Liver disease, hepatitis and jaundice (especially with prolonged use).

Skin and subcutaneous tissue diseases

Uncommon: Eczema, pruritus, urticaria

Rare: Skin rash with or without irritation, hypersensitivity reactions, cross-reaction with other sympathomimetics, allergic dermatitis*

*Several allergic skin reactions with or without systemic symptoms such as bronchospasm and angioedema have been reported following the use of pseudoephedrine.

Very rare: Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

Kidney and urinary tract diseases

Uncommon: dysuria, urinary retention in male patients (pre-existing prostatic enlargement may be a predisposing factor).

Very rare: Decreased urea excretion, increased serum urea concentration, papillary necrosis, acute renal failure, edema, hematuria, interstitial nephritis, proteinuria

General disorders and administration site conditions

Very rare: edema, peripheral edema

Studies

Very rare: Increases in liver function tests, decrease in hematocrit and hemoglobin.

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

4.9. Overdose and its treatment

Intake of more than 400 mg/kg in children may cause symptoms. The dose-response effect in adults is less clear. The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients taking clinically significant NSAIDs will experience no more than nausea, vomiting, epigastric pain, or rarely diarrhea. Tinnitus, headache, and gastrointestinal bleeding are also likely. In more severe poisonings, central nervous system toxicity occurs, leading to drowsiness, rarely excitation, and disorientation or coma. Rarely, patients develop convulsions. In severe poisoning, metabolic acidosis may occur and prothrombin time/INR may be prolonged, possibly due to interference with circulating coagulation factors. Acute kidney failure and liver damage may occur. It is possible to have asthma attacks in asthma patients.

Treatment

Treatment should be symptomatic and supportive. It should include maintaining a clean airway and monitoring of cardiac and vital signs until the condition stabilizes. Oral activated charcoal can be administered if the patient shows symptoms within 1 hour after taking a toxic amount of the drug. If frequent and prolonged, convulsions should be treated with intravenous diazepam or lorazepam. For asthma, a bronchodilator should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

pharmacotherapeutic group: Anti-inflammatory and Antirheumatic products

ATC Code: M01AE51

Ibuprofen; It is a phenylpropionic acid derivative non-steroidal anti-inflammatory drug with analgesic, anti-inflammatory and antipyretic effects. It shows its effect by inhibiting cyclooxygenase enzymes, and thus prostaglandin synthesis, as in other nonsteroidal anti-inflammatory drugs. Ibuprofen exerts its antipyretic effect through the hypothalamus.

Like other NSAIDs, ibuprofen can prolong bleeding time by inhibiting platelet aggregation. However, this effect is not permanent like aspirin and is seen as long as the drug is in circulation. Therefore, the use of aspirin together with drugs that inhibit platelet aggregation may increase the risk of bleeding. Use should be avoided as much as possible in conditions such as hemophilia, von Willebrand disease, severe thrombocytopenia (platelet count $<50,000/mm^3$), use of anticoagulants and excessive alcohol intake.

It has been shown that the analgesic effect of ibuprofen begins within 15 minutes, the antipyretic effect begins within 30 minutes, and both effects continue for more than 6 hours.

Experimental data indicate that, when used concomitantly, ibuprofen can competitively inhibit the effect of low-dose acetylsalicylic acid on platelet aggregation. In some pharmacodynamic studies, a reduced effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation has been observed when a single dose of 400 mg ibuprofen is taken within 8 hours before or 30 minutes after an immediate-release acetylsalicylic acid dose (81 mg). Although there are uncertainties regarding the clinical extrapolation of these data, the possibility that prolonged and continued use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. A clinically significant effect is unlikely to be expected with occasional use of ibuprofen (see section 4.5).

Pseudoephedrine hydrochloride; It is a sympathomimetic/decongestant agent.
It creates vasoconstriction by directly affecting alpha adrenergic receptors in the respiratory tract mucosa. Thus, hyperemia, edema and congestion in the swollen nasal mucosa are reduced and nasal respiratory capacity is increased.
Pseudoephedrine hydrochloride also increases the drainage of sinus secretions and may open up a blocked Eustachian tube.
It is a stereoisomer of ephedrine and has a similar effect. It is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has alpha and beta adrenergic

activities and has a stimulating effect on the central nervous system. It has a longer duration but less potent effect than adrenaline. However, pseudoephedrine has been reported to have less suppressive and central nervous system effects compared to ephedrine.

5.2. Pharmacokinetic properties

General properties

Absorbation:

When ibuprofen is taken orally, it is easily absorbed from the gastrointestinal tract, reaching peak serum concentrations within 1-2 hours.

The mean plasma concentration is reached rapidly at 70 minutes after administration. Peak plasma levels may be delayed when taken with food. The plasma half-life is about 2 hours.

Pseudoephedrine is rapidly and completely absorbed from the gastrointestinal tract. In healthy adult volunteers, administration of 60 mg of pseudoephedrine produced a peak plasma concentration (Cmax) of approximately 180 ng/ml after approximately 1.5 hours (Tmax). It reaches its decongestant effect within 30 minutes, which lasts for 4 hours. The plasma half-life is about 5.5 hours.

Distribution:

Ibuprofen is 99% bound to plasma proteins. The apparent volume of distribution (Vd/F) of pseudoephedrine is 2.8 l/kg.

Biotransformation:

After oral administration, ibuprofen is metabolized in the liver and is completely excreted in the urine as hydroxyl (25%) and carboxypropyl (37%) phenylpropionic acid metabolites within 24 hours after the last dose.

Pseudoephedrine is partially metabolized to an active metabolite, norpseudoephedrine, by N-demethylation in the liver. Pseudoephedrine and its metabolite are excreted in the urine, with 55 to 90% of the dose being excreted unchanged.

Elimination:

Approximately 75-85% of an oral dose of ibuprofen is almost completely eliminated 24 hours after the last dose, with the remainder in the faeces.

The total body clearance (Cl/F) of pseudoephedrine is approximately 7.5 ml/min/kg. When the urine is acidified, the rate of urinary excretion of pseudoephedrine increases. Conversely, as urine pH increases, urinary excretion rate decreases.

Linearity/non-linearity:

Pseudoephedrine showed linear pharmacokinetics in the concentration range of 1.0-800 ng/ml. Following oral administration, ibuprofen is rapidly and almost completely absorbed. Peak serum levels are achieved between 1 and 2 hours after dosing. Although there is a linear relationship between free ibuprofen plasma concentration and dose, the relationship between administered dose and the total area of the ibuprofen concentration-time curve appears to be non-linear. The total urinary excretion of ibuprofen and its metabolites is a linear function of dosage. The absorption and excretion of ibuprofen is not affected by the dosing regimen at doses between 50 mg and 600 mg.

Characteristics in patients

Kidney failure:

Elimination of ibuprofen metabolites may be reduced in patients with renal impairment. Elimination of pseudoephedrine may be reduced in patients with renal impairment.

Liver failure:

Ibuprofen is eliminated mainly by hepatic metabolism. Therefore, in those with liver disease; ibuprofen doses may need to be reduced compared to patients with normal hepatic function.
There are no specific studies with pseudoephedrine in patients with hepatic impairment.

Geriatric population:

There was no significant change in the pharmacokinetics of ibuprofen in the geriatric population.
Elimination of pseudoephedrine may be reduced in elderly patients.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity for ibuprofen. Effects in non-clinical studies were achieved only at exposures sufficiently above the maximum human exposure that appeared to be of little relevance to clinical use.

It was determined that pseudoephedrine was not genotoxic in *in vivo* and *in vitro* tests performed on bacteria and mammals.

There is not enough information about whether pseudoephedrine has carcinogenic potential.

Pseudoephedrine was not teratogenic up to an oral dose of 432 mg/kg/day in rats or an oral dose of 200 mg/kg/day in rabbits.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Calcium hydrogen phosphate anhydrate
Microcrystalline cellulose
croscarmellose sodium
Povidone K-30
colloidal anhydrous silica
magnesium stearate

6.2. Incompatibilities

Not reported.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 25˚C.

6.5. The nature and content of the packaging

It is presented in blister packs of 20 and 24 tablets.

6.6. Disposal of residues from the medicinal product for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORISATION HOLDER

Drogsan İlaçları San. ve Tic. A.Ş.
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06520 Balgat-ANKARA
Tel: 0 312 287 74 10
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8. MARKETING AUTHORISATION NUMBER

254/1 (in Turkey)

9. FIRST LICENSE DATE / LICENSE RENEWAL DATE

First license date: 08.10.2013
License renewal date: 07.10.2019

10. RENEWAL DATE OF SPC

16/11/2018