SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 200 mg/5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ibuprofen 200 mg and phenylephrine hydrochloride 5.0 mg.
Excipient with known effect: sodium.
Each film-coated tablet contains 0.74 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Description: white to off- white biconvex film-coated tablets with diameter of approx. 10.6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The product is designed for the relief of symptoms of cold and influenza with associated congestion including aches and pain, headache, fever, sore throat, blocked nose and sinuses.

4.2 Posology and method of administration

For oral administration and short-term use only.

Posology

Adults and adolescents aged 12 years and over:
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. Adults should consult a doctor if symptoms persist or worsen, or if the product is required for more than 3-5 days.
If in adolescents (aged 12 years and over) this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Two tablets every 8 hours. Leave at least 4 hours between doses and do not exceed six tablets in any 24 hour period.

The product is not intended for children under 12 years.

Elderly
In elderly patients the dosage is the same like in adults, but increased caution is necessary (see section 4.4).

Method of administration
The tablet may be taken with or without food. If taken with food or shortly after eating, the onset of action may be delayed. However, taking it with food improves tolerability of the product and reduces probability of gastrointestinal problems.

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

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes or proven ulceration or bleeding).
- Severe hypertension, renal or hepatic failure, severe heart failure (NYHA Class IV) (see section 4.4).
- Disorders of haemocoagulation and haemopoiesis.
- Third trimester of pregnancy.
- Hyperthyroidism.
- Diabetes mellitus.
- Narrow-angle glaucoma.
- Urinary retention.
- Phaeochromocytoma.
- Patients who are currently taking tricyclic antidepressants or other sympathomimetic drugs, beta-blockers, and those who are currently taking or have taken monoamine oxidase inhibitors within the last two weeks.

4.4 Special warnings and precautions for use

Ibuprofen
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see gastrointestinal and cardiovascular risks below).

Elderly
The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Gastrointestinal (GI) bleeding, ulceration and perforation

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.
In patients with increased risk of adverse reactions together with those on long term treatment with acetylsalicylic acid in antiaggregation doses or other drugs which increase GI risk (see section 4.5) concomitant use of protective agents such as misoprostol or proton pump inhibitors should be considered.

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelets agents such as aspirin (see section 4.5).

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

Other NSAIDs
The use of this product with concomitant NSAIDs, including cyclo-oxygenase-2 selective inhibitors, should be avoided (see section 4.5).

Cardiovascular and cerebrovascular effects
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2,400 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. ≤ 1,200 mg/day) is associated with an increased risk of arterial thrombotic events.
Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2,400 mg/day) should be avoided.
Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2,400 mg/day) are required.

Dermatological
Serious skin reactions, some of them fatal, including exfoliating dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk 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. This medicine should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Respiratory
Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.
Increased attention is necessary in patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

SLE and mixed connective tissue disease
Systemic lupus erythematosus and mixed connective tissue disease - increased risk of aseptic meningitis (see section 4.8).

Renal impairment
Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8).

Hepatic impairment
Hepatic dysfunction (see sections 4.3 and 4.8).

Impaired female fertility
There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered (see section 4.6).

Increased attention is necessary directly after major surgery.

Drinking of alcoholic beverages and smoking is not suitable during treatment.

Paediatric population
There is a risk of renal impairment in dehydrated children and adolescents.

<u>Phenylephrine</u>
Phenylephrine should be used with care in men with prostate hypertrophy as they may be predisposed to urinary retention.
The physician or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes, i.e. orally and topically (nasal, aural and eye preparations).

<u>Excipients</u>

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen

Ibuprofen should not be used in combination with:

- *Acetylsalicylic acid:* Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).
- *Other NSAIDs including cyclo-oxygenase-2 selective inhibitors:* Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse reactions (see section 4.4).

Ibuprofen should be used with caution in combination with:

- *Anti-coagulants:* NSAIDs may enhance the effects of anticoagulants such as warfarin (see section 4.4).
- *Antihypertensives and diuretics:* NSAIDs may diminish the effect of these drugs. Diuretics can increase the risk of nephrotoxicity.
- *Potassium sparing diuretics*: the concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
- *Corticosteroids:* increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- *Anti-platelet agents and selective serotonin-reuptake inhibitors (SSRIs):* increased risk of gastrointestinal bleeding (see section 4.4).
- *Cardiac glycosides:* NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- *Lithium, phenytoin, methotrexat, baclofen:* there are clinical data indicating that NSAIDs may increase plasma level of these drugs.
- *Cyclosporin, tacrolimus*: may increase the risk of nephrotoxicity on account of reduced synthesis of prostaglandins in the kidney. During combination treatment renal function must be closely monitored, especially in the elderly.
- *Zidovudine:* increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- *Quinolone antibiotics:* animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- *Sulfinpyrazone, probenecid:* ibuprofen may reduce uricosuric effect of these drugs.
- *Sulphonylurea derivatives:* concomitant use with ibuprofen may increase risk of hypoglycemia.
- *Aminoglycosides:* since ibuprofen may decrease the clearance of aminoglycosides, their co-administration may increase the risk of nephrotoxicity and ototoxicity.

- *Mifepristone:* NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Phenylephrine

Phenylephrine should not be used in combination with:
- *Antidepressants*: MAO inhibitors increase the effect of phenylephrine. Concomitant use of phenylephrine with MAO inhibitors and tricyclic antidepressants can lead to hypertensive crisis. Phenylephrine may enhance anticholinergic effect of tricyclic antidepressants.
- *Beta-blockers, antihypertensive drugs, methyldopa and reserpine*: concomitant use of phenylephrine with these drugs can cause a hypertensive crisis.

Phenylephrine should be used with caution in combination with:
- *Sympathomimetics and vasodilators*: phenylephrine may adversely interact with other sympathomimetics and vasodilators.
- *Digitalis glycosides:* concomitant use with digitalis glycosides increases the risk of abnormal heart rhythm.
- *Ergot alkaloids:* Concomitant use with ergot alkaloids (ergotamine and methysergide) increases the risk of ergotism.

4.6 Fertility, pregnancy and lactation

Ibuprofen

Pregnancy
Inhibition of prostaglandin synthesis can unfavourably affect pregnancy and/or the development of embryos or foetuses. Data from epidemiological studies have indicated an enhanced risk of abortions, cardiac malformations after use of prostaglandin synthesis inhibitors in early pregnancy. The absolute risk of cardiovascular malformations was enhanced from less than 1 % to approximately 1.5 %. The risk increases with a dose and length of treatment. In animals, the administration of prostaglandin synthesis inhibitors has indicated elevation of pre- and post-implantation losses and embryonic/foetal lethality. In addition, an elevated incidence of various malformations, including cardiovascular ones, has been described in animals treated with prostaglandin synthesis inhibitors during organogenesis.

If not explicitly inevitable, ibuprofen must not be administered in the course of the first and second trimesters of pregnancy. If ibuprofen is used by a woman who tries to become pregnant or during the first and second trimesters of pregnancy, the dose must be as low as possible and the length of treatment must be as short as possible.

In the course of the third trimester of gravidity, all prostaglandin synthesis inhibitors can expose the foetus to the following:
- cardiopulmonary toxicity (with a premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction which may progress up to renal failure with oligohydramnios;

mother and the neonate at the end of pregnancy can be exposed to

- a potential prolongation of the time of bleeding,
- to an inhibition of uterine contractions leading to delayed or protracted parturition.

Due to these facts, ibuprofen is contraindicated during the third trimester of pregnancy.

Breast-feeding
Ibuprofen and its metabolites penetrate to the milk of breast-feeding mothers at extremely low concentrations (according to one study the breastfed child would receive in mother's milk only 0.0008 % of maternal weight-adjusted dosage). Due to minimal amount in breast milk, short elimination half-life and no records till now concerning harmful influence on infants, ibuprofen may be used during breast-feeding for short-term treatment of pain or inflammation signs. Safety after long-term use has not been established.

Fertility
There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

Phenylephrine

Pregnancy
Due to the vasoconstrictive properties of phenylephrine the product should be used with caution in patients with history of pre-eclampsia. Phenylephrine may reduce placental perfusion and the product should be used in pregnancy only if the benefits outweigh this risk.

Breast-feeding
Based on published data available on phenylephrine, it is not contraindicated during breast feeding. Animal data indicate that phenylephrine can decrease milk production, and therefore its use is not advisable at the beginning of lactation, within breast-feeding of newborns and especially premature babies.

Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

Product has no influence on the ability to drive and operate machinery. However, in susceptible individuals it may induce dizziness. Patients should be advised not to drive or operate machinery if affected by dizziness.

4.8 Undesirable effects

The following tables summarise adverse drug reactions of ibuprofen and phenylephrine divided into groups according to MedDRA terminology together with their frequency: very common

(≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to < 1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

TAB 1. Adverse reactions to ibuprofen

MedDRA system organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Very rare	Anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis[1]
Immune system disorders	Uncommon	Hypersensitivity reactions – urticaria, pruritus
	Very rare	Severe hypersensitivity reactions – face, tongue and laryngeal oedema, anaphylaxis, anaphylactic shock[2], angioedema
Psychiatric disorders	Very rare	Depression, insomnia
Nervous system disorders	Uncommon	Headache, dizziness, tinnitus
	Rare	Aseptic meningitis
Eye disorders	Rare	Vision disorders, colour blindness, amblyopia
Cardiac disorders	Very rare	Palpitations, cardiac failure
Vascular disorders	Very rare	Hypertension
Respiratory, thoracic and mediastinal disorders	Not known	Asthma exacerbation, bronchospasm
Gastrointestinal disorders	Very common	Dyspepsia, nausea, vomiting, diarrhoea, flatulence, constipation
	Common	Abdominal pain
	Rare	Peptic ulcer, perforation and gastrointestinal haemorrhage, melaena, haematemesis
	Very rare	Ulcerative stomatitis, gastritis and mouth ulceration, Crohn's disease and colitis aggravated
Hepatobiliary disorders	Very rare	Liver disorders
Skin and subcutaneous tissue disorders	Uncommon	Various types of rashes
	Very rare	Bullous reactions – Stevens-Johnson

MedDRA system organ class	Frequency	Undesirable effect
		syndrome, erythema multiforme, toxic epidermal necrolysis
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and urinary disorders	Very rare	Cystitis, haematuria, renal function impairment, interstitial nephritis, nephrotic syndrome, acute renal failure[3]

[1] first signs of haematopoetic disorders are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
[2] symptoms of anaphylactic reaction include hypotension, tachycardia and dyspnoe
[3] especially in long-term use, associated with increased serum urea and oedema

TAB 2. Adverse reactions to phenylephrine

MedDRA system organ class	Frequency	Undesirable effect
Psychiatric disorders	Rare	Nervousness
Nervous system disorders	Common	Headache, dizziness, insomnia
Eye disorders	Not known	Eye pain and stinging, blurred vision, photophobia, acute angle closure glaucoma
Cardiac disorders	Very rare	Palpitations
	Not known	Arrhythmias, tachycardia
Vascular disorders	Very rare	Increased blood pressure*
Gastrointestinal disorders	Very rare	Nausea, vomiting, diarrhoea

* reflex bradycardia as a consequence of hypertension after intravenous administration of phenylephrine

The most commonly observed adverse effects are gastrointestinal in nature. Peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, may occur, particularly in the elderly.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2,400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.
In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic

meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation, have been observed (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Ibuprofen
In children, ingestion of more than 400 mg/kg may cause symptoms. In adults, the dose response rate effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms
Patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management
There is no specific antidote.
Therapy of acute overdose: to carry out gastric lavage as soon as possible with administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount and laxative or to evoke vomiting reflex.
Management should be supportive and symptomatic and include control and adjustment of liquid and electrolyte balance, maintenance of respiratory and cardiovascular functions, diazepam or lorazepam can be administered in the case upon convulsions, plasma-expanders, eventually dopamine or norepinephrine during hypotension. Give bronchodilators for asthma.

Phenylephrine
Features of severe overdose of phenylephrine include haemodynamic changes and cardiovascular collapse with respiratory depression.
Treatment includes early gastric lavage and symptomatic and supportive measures.
Hypertensive effects may be treated with an intravenous alpha-receptor blocking agent.

Phenylephrine overdose is likely to result in: nervousness, headache, dizziness, insomnia, increased blood pressure, nausea, vomiting, mydriasis, acute angle closure glaucoma (most likely to occur in those with closed angle glaucoma), tachycardia, palpitations, allergic reactions (e.g. rash, urticaria, allergic dermatitis), dysuria, urinary retention (most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy). In severe cases confusion, hallucinations, seizures and arrhythmias may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, ATC code: M01AE51 - ibuprofen, combinations.

Ibuprofen
Ibuprofen, derivative of propionic acid, is a non-steroidal antirheumatic with good analgesic, anti-inflammatory, and antipyretic effect. It has analgesic effect at lower doses, anti-inflammatory at higher doses. Anti-inflammatory effect is due to the inhibition of cyclooxygenase with the following inhibition of prostaglandin biosynthesis. Reduction of the release of pro-inflammatory mediators from granulocytes, basophiles and mastocytes mitigates the inflammation. Furthermore ibuprofen reduces the vessel sensitivity to bradykinin and histamine, it affects lymphokine production in T lymphocytes and it inhibits vasodilatation. It also inhibits thrombocyte aggregation.
Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Onset of analgesic effect is after 0.5 hour, maximal antipyretic effect is achieved after 2-4 hours. Antipyretic effect persists for 4-8 hours or even more hours, analgesic effect 4-6 hours.

Phenylephrine
Phenylephrine is a post-synaptic alpha-receptor agonist with low cardioselective beta-receptor affinity and minimal central stimulant activity. It is a recognised decongestant and acts by vasoconstriction to reduce oedema and nasal swelling.

5.2 Pharmacokinetic properties

Ibuprofen
It is quickly and well absorbed after oral administration, peak plasma concentration is achieved already after 45 minutes upon administration on empty stomach, when administered with meal after circa 1–3 hours. Ibuprofen is absorbed more slowly after rectal application, maximal serum concentration is achieved 2 hours after application. Ibuprofen is bound to plasma proteins, but the binding is reversible. It is relatively quickly metabolized in the liver and excreted by urine, mainly in the form of metabolites and their conjugates, minor part is excreted by bile into the feaces. Biological half-life is about 2 hours. Drug accumulation in the organism may occur in the case of decreased excretion. Ibuprofen excretion is finished 24 hours after the administration of

the last dose. Presence of meal minimally alters its bioavailability. Ibuprofen passes through placental barrier, it is excreted into the breast milk at amount lower than 1 μg/ml.

Phenylephrine
Pre-systemic metabolism is high at about 60 %, resulting in systemic bioavailability of about 40 %. Peak plasma levels occur between 1 and 2 hours and the plasma half-life ranges between 2–3 hours. When taken by mouth as a nasal decongestant phenylephrine is usually given at intervals of 4–6 hours.

5.3 Preclinical safety data

Ibuprofen
The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal tract. *In vitro* and *in vivo* studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat, mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta. Following administration of maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed in the progeny of rats.

Phenylephrine
Acute toxicity of phenylephrine (LD_{50}) is 120 mg/kg body weight in mice, but 350 mg/kg body weight in rats. Specific manifestations of toxicity have not been observed in animals after administration of phenylephrine.
Genotoxicity studies with phenylephrine have led to ambiguous results. Carcinogenic potential has not been observed in rodents after administration of phenylephrine.
Data on reproductive toxicity and foetotoxicity after administration of phenylephrine to animals are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Maize starch, pregelatinised
Sodium starch glycolate (type A)
Talc
Povidone 30
Silica, colloidal anhydrous
Stearic acid 50
Hypromellose 2910/5
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister (transparent PVC/Al foil), paper folding box
Size of packaging: 12 and 24 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 200 mg/5 mg film-coated tablets
ibuprofen, phenylephrine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains ibuprofen 200 mg and phenylephrine hydrochloride 5 mg.

3. LIST OF EXCIPIENTS

Contains sodium.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets
12 coated tablets
24 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally – MAH name, town, country]

12. MARKETING AUTHORISATION NUMBER(S)

Reg.No.:

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

15. INSTRUCTIONS ON USE

For flu and cold

- Fever
- Blocked nose and painful sinuses
- Headache
- Sore throat

[Invented name] relieves symptoms of influenza and cold, including fever, headache, painful sinuses, sore throat and muscle and joint pain. Moreover, it helps with runny nose, relieves stuffy nose and nasal sinuses, facilitating breathing.
Adults and adolescents aged 12 years and over: usual dosage is 2 tablets every 8 hours. The maximum daily dose is 6 tablets in 24 hours.

16. INFORMATION IN BRAILLE

[To be completed nationally - Invented name (if needed + strength + pharmaceutical form)]

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON THE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 200 mg/5 mg film-coated tablets
ibuprofen, phenylephrine hydrochloride

2. NAME OF THE MARKETING HOLDER

Logo MAH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Package leaflet: information for the patient

[Invented name] 200 mg/5 mg film-coated tablets
Ibuprofen, phenylephrine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if you do not feel better or if you feel worse after 3 days in adolescants and after 3-5 days in adults.

What is in this leaflet

1. What [Invented name] is and what it is used for

[Invented name] contains ibuprofen and phenylephrine hydrochloride, which are effective in relieving the symptoms of influenza and cold, including fever, headache, painful sinuses, sore throat and muscle and joint pain. Moreover, it helps with runny nose, relieves stuffy nose and nasal sinuses, facilitating breathing.
Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) and is effective against aches and pains (including headache), swelling and can also reduce a fever. Phenylephrine hydrochloride (nasal decongestant) reduces swelling in the passages of the nose, relieving nasal congestion and reducing the pressure which may cause a headache.

Take [Invented name] only if you have colds or influenza accompanied by stuffy nose. If you do not have stuffy nose, monocomponent products containing only ibuprofen should be preferred.
The product is intended for adults and adolescents aged 12 years and over.

2. What you need to know before you take [Invented name]

Do not take [Invented name] if you

- are allergic to ibuprofen, phenylephrine hydrochloride or any of the other ingredients of this medicine (listed in section 6) and at hypersensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs manifested as shortness of breath, asthma or urticaria,
- have active or recurrent ulcer or bleeding to the stomach or duodenum or if you have ever had it repeatedly (i.e. at least twice) in the past,
- have ever had gastrointestinal bleeding or perforation, related to previous NSAIDs therapy,
- suffer from disorder of blood formation or disorder of blood clotting,
- have severe high blood pressure or severe heart, liver or kidney failure,
- are a woman in the third trimester of pregnancy,
- have diabetes,
- have an overactive thyroid gland (hyperthyroidism),
- have narrow-angle glaucoma,
- have urinary retention (lack of ability to urinate),
- have a vascular tumour near your kidney (pheochromocytoma),
- are currently taking:
  - medicines used to treat depression (from the group of monoamine oxidase inhibitors, MAOIs) or you have taken them within the last two weeks,
  - medicines used to treat depression (from the group of tricyclic antidepressants),
  - medicines used to treat high blood pressure or heart disease (from the group of beta-blockers),
  - sympathomimetics (medicine for the relief of congestion of the mucous membranes) including the medicines administered by several routes, i.e. orally and topically (nasal, aural and eye medicines).

If you are not sure whether any of the conditions mentioned above applies to you, ask your doctor.

Warnings and precautions
You should discuss your treatment with your doctor or pharmacist before taking [Invented name] if you:
- have or have ever had bowel problems,
- suffer from inflammatory ulcerous disease of digestive tract such as Crohn´s disease or ulcerative colitis,
- suffer from kidney or liver disorder,
- suffer from bronchial asthma, hay fever, nasal polyps or chronic obstructive respiratory disorders,
- directly after major surgery,
- suffer from systemic lupus erythematodes (immunity system disorder) and other disorders of the connective tissue (the risk of aseptic meningitis),
- have heart problems including heart failure, angina (chest pain), or if you have had a heart attack, bypass surgery, peripheral artery disease (poor circulation in the legs of feet due to narrow or blocked arteries), or any kind of stroke (including 'mini-stroke' or transient ischaemic attack "TIA"),
- have high blood pressure, diabetes, high cholesterol, have a family history of heart disease or stroke, or if you are a smoker.
- are a man with prostate enlargement (prostate hypertrophy).

Anti-inflammatory/pain-killer medicines like ibuprofen may be associated with a small increased risk of heart attack or stroke, particularly when used at high doses. Do not exceed the recommended dose or duration of treatment.
Some concomitant medications could increase the risk of gastrotoxicity or bleeding (other non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs), or anti-platelet agents such as acetylsalicylic acid).
In patients with increased risk of gastrointestinal toxicity concomitant use of protective agents should be considered.

If you previously had gastrointestinal toxicity, particularly when elderly, you should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment to your doctor.

Children and adolescents
The product is not intended for children under 12 years.
There is a risk of renal impairment in dehydrated children and adolescents.

Other medicines and [Invented name]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take [Invented name], if you are taking:
- any other medicines containing acetylsalicylic acid or other NSAIDs,
- medicines for cold and flu,
- medicines for treating nasal congestion (stuffy nose),
- or have taken antidepressants within the last two weeks (see section "Do not take [Invented name]" above),
- sympathomimetic drugs (see section "Do not take [Invented name]" above),
- medicines used to treat high blood pressure or heart diseases (from the group of beta-blockers) (see section "Do not take [Invented name]" above).

[Invented name] may affect or be affected by some other medicines. For example:
- corticosteroids,
- medicines that reduce high blood pressure (ACE-inhibitors such as captopril, beta-blockers such as atenolol medicines, angiotensin-II receptor antagonists such as losartan) and water tablets,
- medicines that are anti-coagulants (i.e. thin blood/prevent clotting e.g. aspirin/acetylsalicylic acid, warfarin, ticlopidine),
- selective serotonin reuptake inhibitors (SSRIs) (medicines used for depression),
- some of antibiotics (quinolone, aminoglycosides),
- sulphonylurea derivatives (antidiabetic drugs),
- products containing lithium (a medicine for manic depressive illness and depression), methotrexate (a medicine for cancer or rheumatism), sulfinpyrazone and probenecid (medicines for gout), cyclosporin and tacrolimus (immunosuppressive medicines), zidovudine (a medicine for treating AIDS), digoxin (for heart insufficiency), phenytoin (for

epilepsy), baclofen (used for treating spasm of skeletal muscles), ergotamine and methysergide (drugs used in the treatment of migraine attack), mifepristone (the abortion pill).

Some other medicines may also affect or be affected by the treatment of [Invented name]. You should therefore always seek the advice of your doctor or pharmacist before you use [Invented name] with other medicines.

[Invented name] with food, drink and alcohol
The tablet may be taken with or without food. If taken with food or shortly after eating, the onset of action may be delayed. However taking it with food improves tolerability of the medicine and reduces probability of gastrointestinal problems. Drinking of alcoholic beverages and smoking is not suitable during treatment.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. [Invented name] is not recommended for pregnant and breast-feeding women.
The product belongs to a group of medicines (NSAIDs) which may impair the fertility in women. This effect is reversible on stopping the medicine.

Driving and using machines
[Invented name] has no influence on the ability to drive or operate machinery. However, for some people, this medicine may cause dizziness, thereby it may adversely affect activities requiring increased attention. Do not drive or use machines if this happens to you.

<Invented name> contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take [Invented name]

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults and adolescents aged 12 years and over:
This medicine is intended for short-term use only. You should take the lowest dose for the shortest time necessary to relieve your symptoms. Usual dose is 2 tablets every 8 hours. Leave at least 4 hours between doses and **do not take more than 6 tablets per 24 hours.**

Do not take this medicine for more than 3-5 days without consulting your physician.
If you are an adult and your signs of illness do not resolve, or if they worsen or persist longer than 3-5 days, you should consult your doctor. If in adolescents (12 years of age and above) this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.
Do not exceed the recommended dose or duration of treatment.

Tablets should be swallowed as a whole and followed with a sufficient amount of liquid. It is important to drink plenty of fluids when suffering from colds and flu.

Elderly
In elderly patients the dosage is the same like in adults, but increased caution is necessary (see section "Warnings and precautions" above)

Patients with impaired liver or kidney function
In patients with liver and kidney insufficiency increased caution is necessary (see section "Warnings and precautions" above).

If you take more [Invented name] than you should
If you have taken more [Invented name] than you should, or if children have taken medicine by accident always contact a doctor or nearest hospital to get an opinion of the risk and advice on action to be taken.
The symptoms can include nausea, stomach pain, vomiting (may be blood streaked), headache, ringing in the ears, confusion and shaky eye movement. At high doses, drowsiness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, cold body feeling, and breathing problems have been reported.
If you forget to take [Invented name]
If you forget to take a dose, take the next dose as soon as you remember, provided that you took the last dose at least 4 hours ago. Do not take a double dose to make up for a forgotten tablet dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

There is an increased probability of side effects occurring in the elderly, people with a history of stomach or duodenal ulcers (mainly with bleeding or mucosa perforation) or in people receiving long-term treatment with products containing acetylsalicylic acid.

Stop taking this medicine and seek immediate medical attention if you experience the following:

- Serious allergic reactions (including potentially fatal anaphylactic shock) which can cause skin rash, swelling of the face, lips, mouth, tongue or throat, wheezing or difficulty breathing. Very rare frequency of occurrence.
- Serious skin reaction with purplish spots or patches on the skin, blisters, peeling of the skin, (high) fever, joint pain and/or eye inflammation (Stevens Johnson syndrome/toxic epidermal necrolysis). Very rare frequency of occurrence.

- Severe reduction in number of white blood cells which makes infections more likely, high fever, lesions of the mucous membranes and skin. Very rare frequency of occurrence.
- Digestive problems such as pain in stomach or other abnormal stomach symptoms (common frequency of occurrence); pass bloody or black stools, vomit any blood or dark particles that look like coffee grounds (rare frequency of occurrence).

The other side effects which may occur are listed below grouped according to the frequency:

Very common (may affect more than 1 in 10 people):
- Indigestion, feeling sick (nausea), being sick (vomiting), diarrhoea, wind, constipation.

Common (may affect up to 1 in 10 people):
- Headache, dizziness, inability to fall asleep (insomnia).

Uncommon (may affect up to 1 in 100 people):
- Urticaria, itching, rash.
- Ringing in the ears.

Rare (may affect up to 1 in 1,000 people):
- Inflammation of the protective membranes covering the brain and spinal cord (meningitis).
- Vision disorders, colour blindness.
- Ulceration or rupture in the stomach, gullet or intestines, dark or black stools and vomiting of blood.
- Nervousness.

Very rare (may affect up to 1 in 10,000 people):
- Depression.
- Feeling your heartbeat, heart failure, increased blood pressure.
- Blood disorders (first signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, fatigue, unexplained bleeding and bruising).
- Mouth ulcers, stomach inflammation, worsening of existing bowel disease (colitis or Crohn's disease).
- Liver or kidney problems (possible kidney failure, inflammation of the kidneys), blood in the urine, bladder inflammation.

Not known (frequency cannot be estimated from the available data):
- Irregular or faster heartbeat, slow heartbeat (as a consequence of increased blood pressure after intravenous administration of phenylephrine).
- Eye pain and stinging, blurred vision, sensitivity to or intolerance of light, acute angle closure glaucoma (eye pain).
- Difficulty in breathing or wheezing (predominantly in patients with bronchial asthma), aggravation of asthma.
- A severe skin reaction known as DRESS syndrome can occur. Symptoms of DRESS include: skin rash, fever, swelling of lymph nodes and an increase of eosinophils (a type of white blood cells).

Medicines such as [Invented name] may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [Invented name]

Keep this medicine out of the sight and reach of children.
Store below 25°C. Store in the original package in order to protect from light.
Do not use this medicine after the expiry date which is stated on the package after EXP.
The expiry date refers to the last day of that month.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Invented name] contains
The active substances are ibuprofen 200 mg and phenylephrine hydrochloride 5 mg in each tablet.
The other ingredients are maize starch, maize starch pregelatinised, sodium starch glycolate (type A), talc, povidone 30, silica, colloidal anhydrous, stearic acid 50, hypromellose 2910/5, macrogol 6000, titanium dioxide (E171).

What [Invented name] looks like and contents of the pack
[Invented name] are white to off- white biconvex film-coated tablets with diameter of approx. 10.6 mm.
Pack size: 12 and 24 film-coated tablets.
Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer
[To be completed nationally]

This medicinal product is authorized in the Member States of the EEA under the following names: Ibalgin Grip in the Czech Republic and Slovak Republic, MODAFEN GRIP in Poland, Ibuprofen + phenylephrine Sanofi-aventis in Luxembourg.

This leaflet was last revised in