1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

DECLOZIT 200 mg/30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of DECLOZIT contains 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride.

Contains sugar: Lactose monohydrate 6,7 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

DECLOZIT is a brown to light brown colour, modified capsule shape, biconvex film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DECLOZIT is indicated for the relief of symptoms associated with the common cold, sinusitis, or flu, including nasal congestion, headache, fever, body aches and pain.

4.2. Posology and method of administration

Posology

Adults and children 12 years and older:

Take one tablet every 4 to 6 hours. If symptoms do not respond to one tablet, a second tablet may be taken. Do not exceed 6 tablets in 24 hours.

Do not take for cold for more than 7 days or for fever for more than 3 days, unless directed by a doctor. If the cold or fever persists or gets worse, or if new symptoms occur, consult a doctor.

Use the lowest effective dose for the shortest possible duration of treatment.

Paediatric population

DECLOZIT is not to be given to children under 12 years.

Method of administration

For oral administration.

DECLOZIT should be taken with a glass of water, with food or after meals.

4.3. Contraindications

DECLOZIT is contraindicated in:

- Patients with hypersensitivity to ibuprofen, pseudoephedrine hydrochloride or to any excipients in DECLOZIT (see section 6.1), or to any other Nonsteroidal anti-inflammatory drugs (NSAIDs), or to any other sympathomimetic medicines.
- Patients who have had a severe allergic reaction to aspirin such as asthma, swelling, shock or hives, because even though DECLOZIT contains no aspirin, or salicylates, cross-reactions may occur in patients allergic to aspirin.
- Cardiovascular disease, heart failure, history of myocardial infarction (see section 4.4).
- Hypertension (see section 4.4).

- Diabetes mellitus.
- Hyperthyroidism.
- Hyperexcitability.
- Prostatic hypertrophy.
- Phaeochromocytoma.
- Glaucoma.
- History of seizures.
- Systemic lupus erythematosus (see section 4.4).
- History of stroke or presence of risk factors for stroke (due to the α-sympathomimetic activity of pseudoephedrine hydrochloride, as contained in DECLOZIT).
- Patients with impaired renal and liver functions.
- Patients with a history of gastrointestinal perforation, ulceration or bleeding (PUB) related to previous NSAIDs use.
- Patients with active or history of recurrent ulcer, haemorrhage or perforations.
- Patients with bleeding disorders, haematological disorders.
- Pregnancy and lactation (see section 4.6). NSAID use in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).
- Children under 12 years (see section 4.2).
- Patients being treated with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping such treatment (see section 4.5).
- Concomitant use of other vasoconstrictor medicines used as nasal decongestants, whether administered orally or nasally (e.g. phenylpropanolamine, phenylephrine and ephedrine), and methylphenidate (see section 4.5).

4.4. Special warnings and precautions for use

Hypersensitivity

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported. DECLOZIT should be discontinued at the first appearance of rash, mucosal lesions, or any other signs of hypersensitivity.

Drug Reaction with Eosinophillia and Systemic symptoms

Drug reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking non-steroidal anti-inflammatory therapy (NSAIDs) such as DECLOZIT. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue DECLOZIT and evaluate the patient immediately.

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) may occur with ibuprofen and pseudoephedrine-containing medicines, such as DECLOZIT (see section 4.8). This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or

many small pustules are observed, administration of DECLOZIT should be discontinued and appropriate measures taken if needed.

Other similar medicines

DECLOZIT should not be combined with other non-prescription pain relievers, any other ibuprofen-containing medicines, or other NSAIDs including cyclo-oxygenase (COX)-2 selective inhibitors (see section 4.5).

Hypertension and/or heart failure

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with non-steroidal anti-inflammatory therapy, including DECLOZIT.

In view of the inherent potential of DECLOZIT to cause fluid retention, heart failure may be precipitated in some compromised patients (see section 4.3).

Gastrointestinal effects

Gastrointestinal perforation, ulceration or bleeding (PUB), 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 gastrointestinal events.

The elderly has an increased frequency of adverse reactions to NSAIDs, such as DECLOZIT, especially gastrointestinal PUBs, which may be fatal. The risk of gastrointestinal bleeding or ulceration is higher with increasing doses, in patients with a history of ulcers and the elderly.

These patients should commence treatment on the lowest dose available. Combination therapy with protective medicines (e.g. misoprostol or proton pump inhibitors) should be

considered for these patients and also for patients taking concomitant low-dose acetylsalicylic acid or other medicines likely to increase gastrointestinal risk (see below and section 4.5).

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

Particular caution is advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) or antiplatelet medicines such as acetylsalicylic acid (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving DECLOZIT, treatment should be stopped.

DECLOZIT should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, peptic ulcer, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Through concomitant consumption of alcohol, undesirable effects may be increased on use of NSAIDs, such as DECLOZIT, particularly those that concern the gastrointestinal tract or the central nervous system.

Ibuprofen:

DECLOZIT should be discontinued in patients who experience blurred or diminished vision or changes in colour vision.

If visual disturbances occur during the course of treatment, a full ophthalmological examination should be carried out.

Aseptic meningitis has occurred in patients with systemic lupus erythematosus who were receiving ibuprofen, as contained in DECLOZIT.

Bronchospasm may be precipitated in patients suffering from, or with a history of bronchial asthma or allergic disease. DECLOZIT should not be taken with cases of asthma without prior consultation with a doctor (see section 4.3).

Patients who have asthma associated with chronic rhinitis, chronic sinusitis and/or nasal polyposis have a higher risk of allergic reactions when taking acetylsalicylic acid and/or NSAIDs. Administration of DECLOZIT may precipitate an acute asthma attack, particularly in some patients who are allergic to acetylsalicylic acid or an NSAID (see section 4.3).

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medicine overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medicines.

Before using DECLOZIT, patients should consult their doctor in case of a blood clotting disorder.

Cardiovascular and cerebrovascular effects

Clinical studies suggest that use of ibuprofen, as contained in DECLOZIT, particularly at a high dose (2 400 mg/day) may be associated with an increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke), and may increase the risk of a cardiovascular adverse event. 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.

NSAIDs should be avoided in patients with established cardiovascular disease, and patients should be informed of the risk of NSAIDs. 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 DECLOZIT 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.

Masking of symptoms of underlying infections

DECLOZIT can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When DECLOZIT is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospitals settings, the patient should consult a doctor if symptoms persist or worsen.

Elderly

The pharmacokinetics of ibuprofen, as contained in DECLOZIT, is not modified by age. No dose adjustment is necessary in the elderly. However, elderly patients should be carefully monitored as they have an increased frequency of NSAID-related undesirable effects, particularly gastrointestinal bleeding and perforation, which can be fatal.

In the initial stages of treatment, careful monitoring of urine output and renal function is required in patients with heart failure, patients with chronically impaired renal or hepatic function, patients taking diuretics, patients who are hypovolaemic as a result of major surgery and, in particular, elderly patients. There is a risk of renal impairment in dehydrated adolescents.

Foetal Toxicity

Regular use of NSAIDs such as DECLOZIT during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased (see section 4.3 and 4.6).

Pseudoephedrine hydrochloride:

To minimise the possibility of insomnia, the last dose for each day should be administered a few hours before bedtime.

Treatment must be discontinued if patients develop hypertension, tachycardia, palpitations, cardiac dysrhythmias, nausea or any neurological signs such as onset or worsening of headache.

Patients should not exceed the recommended dose and/or the recommended duration of treatment. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. Depression may follow rapid withdrawal.

Ischaemic colitis

Some cases of ischaemic colitis have been reported with pseudoephedrine, as contained in DECLOZIT. DECLOZIT should be discontinued, and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy

Cases of ischaemic optic neuropathy have been reported with pseudoephedrine, as contained in DECLOZIT. DECLOZIT should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Before taking DECLOZIT, patients should consult their doctor in case of:

- Hypertension, heart disease, hyperthyroidism, psychosis or diabetes.
- Concomitant administration of antimigraine medicines, especially ergot alkaloid vasoconstrictors (because of the α-sympathomimetic activity of pseudoephedrine).
- Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8).
- Neurological symptoms such as seizures, hallucinations, behavioural disturbances, agitation and insomnia have been described after systemic administration of vasoconstrictors, especially during febrile episodes or on overdose. These symptoms have been more commonly reported in paediatric population.

As a result, it is advisable:

- to avoid administration of DECLOZIT either in combination with medicines which can lower the epileptogenic threshold, such as terpene derivatives, clobutinol, atropine-like medicines and local anaesthetics, or where there is a history of seizures,
- to adhere strictly to the recommended dosage in all cases and to inform the patients about the risks of overdose if DECLOZIT is taken concomitantly with other medicines containing vasoconstrictors.

Patients with urethroprostatic disorders are more prone to develop symptoms like dysuria and urinary retention.

Elderly patients may be more sensitive to the effects on the central nervous system (CNS).

In patients undergoing scheduled surgery in which volatile halogenated anaesthetics are to be used, it is preferable to discontinue treatment with DECLOZIT several days before surgery in view of the risk of acute hypertension (see section 4.5).

Athletes should be informed that treatment with pseudoephedrine hydrochloride, as contained in DECLOZIT, can lead to positive results in doping tests.

Due to the pseudoephedrine hydrochloride component in DECLOZIT, the following conditions are contraindicated (see section 4.3): Severe cardiovascular disorders, coronary heart disease (heart disease, hypertension, angina pectoris), tachycardia, hyperthyroidism, diabetes, pheochromocytoma, history of stroke or presence of risk factors for stroke, history of myocardial infarction.

Interference with serological testing

Pseudoephedrine, as contained in DECLOZIT, has the potential to reduce iobenguane i-131 uptake in neuroendocrine tumours, thus interfering with scintigraphy.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DECLOZIT.

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

4.5. Interaction with other medicines and other forms of interaction

Ibuprofen:

Other NSAIDs, including salicylates and COX-2 selective inhibitors:	The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).
Digoxin:	The concomitant use of DECLOZIT with digoxin preparations may increase serum levels of these medicines. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 days).
Corticosteroids:	Corticosteroids as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal ulceration, perforation or bleeding) (see section 4.3).

Anti-platelet medicines:	Increased risk of gastrointestinal bleeding (see section 4.4).
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 for occasional ibuprofen use (see section 5.1).
Anticoagulants: (e.g.: warfarin, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, iloprost)	NSAIDs, as contained in DECLOZIT, may enhance the effect of anticoagulants (see section 4.4).
	The risk of gastrointestinal bleeding and ulceration associated with DECLOZIT is increased when used with antiplatelets clopidogrel and ticlopidine (see section 4.4).
Phenytoin:	The concomitant use of DECLOZIT with phenytoin medicines may increase serum levels of these medicines. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 4 days).

Selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding and ulceration (see section 4.4).
Lithium:	The concomitant use of DECLOZIT with lithium preparations may increase serum levels of these medicines. A check of serum-lithium is not as a rule required on correct use (maximum over 4 days).
Probenecid and sulfinpyrazone:	Medicines that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
Diuretics, ACE inhibitors, beta-receptor- blockers and angiotensin-II antagonists:	NSAIDs may reduce the effect of diuretics and other antihypertensive medicines. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, beta-receptor-blockers or angiotensin-II antagonists and medicines that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.
	There may also be an increased risk of hyperkalaemia with angiotensin-converting enzyme inhibitors and potassium-sparing diuretics.

	The antihypertensive effects of some antihypertensive medicines including angiotensin-converting enzyme inhibitors, beta blockers, and diuretics may be reduced.
Potassium sparing diuretics:	The concomitant administration of DECLOZIT and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
Methotrexate:	The administration of DECLOZIT within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.
Ciclosporin:	The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain NSAIDs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.
Tacrolimus:	The risk of nephrotoxicity is increased if the two medicines are administered concomitantly.
Zidovudine:	There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Sulphonylureas:	Clinical investigations have shown interactions between NSAIDs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as a precaution on concomitant intake.
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.
Heparins; *Gingko biloba*:	Increased risk of bleeding.
Oral antidiabetic medicines and insulin	DECLOZIT may enhance the effects oral antidiabetic medicines and insulin.
Alcohol, bisphosphonates, or oxpentifylline	The risk of gastrointestinal bleeding and ulceration associated with DECLOZIT is increased when used with alcohol, bisphosphonates, or oxpentifylline (pentoxifylline).

Pseudoephedrine hydrochloride:

Non-selective Monoamine oxidase inhibitors (MAOIs) (iproniazid):	Paroxysmal hypertension, hypertensive crisis and hyperthermia, which can be fatal. Because of the long duration of action of MAOIs, this interaction can occur up to 15 days after discontinuation of the MAOI.
Other indirectly-acting, orally or nasally administered sympathomimetics or vasoconstrictor medicines, α-sympathomimetic medicines, phenylpropanolamine,	Risk of vasoconstriction and/or hypertensive crises.
	In addition to possibly increasing CNS stimulation, concurrent use with other sympathomimetics may increase the cardiovascular effects and the potential for side effects.

phenylephrine, ephedrine, methylphenidate:	
Reversible inhibitors of monoamine oxidase A (RIMAs), linezolid, dopaminergic ergot alkaloids, vasoconstrictor ergot alkaloids:	Risk of vasoconstriction and/or hypertensive crises.
	An increased risk of vasoconstrictor or pressor effects in patients receiving ergot alkaloids.
Oxytocin	An increased risk of vasoconstrictor or pressor effects in patients receiving oxytocin.
Volatile halogenated anaesthetics, halothane:	Perioperative acute hypertension. In scheduled surgery, discontinue treatment with DECLOZIT several days before.
Guanethidine, reserpine and methyldopa:	Effect of pseudoephedrine may be diminished.
Levodopa	May increase the possibility of cardiac dysrhythmias.
Tricyclic antidepressants:	Effect of pseudoephedrine may be diminished or enhanced.
	An increased risk of dysrhythmias may occur.

Digitalis, quinidine or tricyclic antidepressants:	Increased frequency of dysrhythmia.
Antihypertensive medicines	DECLOZIT may reverse the action of many antihypertensive medicines and therefore special care is advisable in patients receiving antihypertensive therapy.
Beta-adrenergic blocking medicines	May inhibit the therapeutic effect of these medicines, with a risk of hypertension and excessive bradycardia and possible heart block.
Citrates	May inhibit urinary excretion and prolong the duration of action of pseudoephedrine, as contained in DECLOZIT.
Central nervous system (CNS) stimulation-producing medicines	Concurrent use may result in additive CNS stimulation to excessive levels.
Nitrates	May reduce the anti-anginal effects of these medicines.
Thyroid medicines	May increase the effects of either these medicines or DECLOZIT.

4.6. Fertility, pregnancy and lactation

The use of DECLOZIT is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential

If DECLOZIT is used by a woman attempting to conceive, the dose should be kept as low and duration of treatment as short as possible.

Pregnancy

Ibuprofen:

Regular use of NSAIDs, such as DECLOZIT, during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased.

Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of prostaglandin synthesis inhibitors in early pregnancy. The risk is believed to increase with dose and duration of therapy.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors, as contained in DECLOZIT, may expose **the foetus** to:

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

Use of NSAIDs, as contained in DECLOZIT, around 20 weeks
gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
Healthcare providers should consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs and follow up according to clinical practice.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors, as contained in DECLOZIT, may expose **the mother and the child, at the end of pregnancy**, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses,
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Pseudoephedrine hydrochloride:

The use of pseudoephedrine hydrochloride decreases maternal uterine blood flow but clinical data are insufficient with respect to effects on pregnancy.
However, studies in animals have shown pseudoephedrine causes a reduction in average weight, length and rate of bone formation in the animal foetus.

Breastfeeding

Pseudoephedrine hydrochloride:

Pseudoephedrine passes into breast milk and may cause unwanted effects in nursing babies.

Considering the potential cardiovascular and neurological effects of vasoconstrictors, ingestion of DECLOZIT is contraindicated during breastfeeding (see section 4.3).

Fertility

There is some evidence that medicines which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

4.7. Effects on ability to drive and use machines

DECLOZIT has moderate influence on the ability to drive or use machines.

Patients who experience dizziness, hallucinations, unusual headaches and visual or hearing disturbances should avoid driving or using machinery (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The most commonly observed adverse reactions related to ibuprofen, as in DECLOZIT, are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration.

Less frequently, gastritis has been observed. In general, the risk of development of adverse reactions (in particular the risk of development of serious gastrointestinal complications) increases with increasing dose and with increasing duration of treatment administration.

Hypersensitivity reactions have been reported following treatment with ibuprofen, as in DECLOZIT. These may consist of:

- Non-specific allergic reaction and anaphylaxis.

- Respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea.
- Assorted skin disorders, including rashes of various types, pruritis, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

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. Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk or arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

b) Tabulated list of adverse reactions

Ibuprofen

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Exacerbation of infectious inflammations (e.g. necrotising fasciitis), aseptic meningitis (stiffness of the neck, headache, nausea, vomiting, fever or disorientation in patients with pre-existent autoimmune diseases (Systemic Lupus Erythematosus (SLE), mixed connective tissue disease)	

Blood and the lymphatic system disorders		Agranulocytosis, anaemia, aplastic anaemia, eosinophilia, leukopenia, neutropenia, thrombocytopenia, haemolytic anaemia,	Ecchymosis
		pancytopenia	
Immune system disorders		Severe generalised hypersensitivity reactions, signs may be facial oedema, angioedema, dyspnoea, tachycardia, drop in blood pressure,	
		anaphylaxis or anaphylactoid reactions, angiitis, bronchospastic allergic reactions, allergic rhinitis, serum sickness-like reaction, systemic lupus erythematosus-like syndrome, hepatotoxicity and aseptic meningitis,	
		urticaria, pruritus and asthma attacks (with drop in blood pressure),	
Psychiatric disorders		Psychotic reactions, depression	
Nervous system disorders	Dizziness	Mild to moderate headache, nervousness or irritability, confusion, hallucinations, aseptic meningitis, peripheral neuropathy, drowsiness, trouble in sleeping,	Convulsions, mood or mental changes
		agitation, tiredness	
Eye disorders		Amblyopia (toxic), blurred or double vision or change in vision, conjunctivitis; dry, irritated or swollen eyes	
Ear and labyrinth disorders		Ringing or buzzing in ears; decrease or change in hearing	

Cardiac disorders		Oedema, hypertension, unexplained nose bleeds; cardiac dysrhythmias; congestive heart failure or exacerbation of; fast or pounding heartbeat; flushing,	Angina pectoris or exacerbation of; pulmonary oedema
		myocardial infarction	
Vascular disorders		Arterial hypertension	
Respiratory, thoracic and mediastinal disorders		Alveolitis, pulmonary eosinophilia, pulmonary oedema	
Gastrointestinal disorders	Mild to moderate abdominal cramps; pain or discomfort; epigastric pain or discomfort; heartburn, nausea,	Decreased appetite or loss of appetite; indigestion, gastritis, melaena, haematemesis, irritation, dryness or soreness of mouth, gingival ulceration or aphthous stomatitis,	Enterocolitis
	Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal,		
	dyspepsia, vomiting, flatulence, diarrhoea, constipation	ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), oesophagitis, pancreatitis, intestinal diaphragm-like stricture	
Hepatobiliary disorders		Hepatitis or jaundice (toxic),	Abnormalities in liver function tests
		hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure	
Skin and subcutaneous tissue disorders	Skin rash	Itching, bullous eruption, hives, Stevens-Johnson syndrome, toxic epidermal necrolysis,	Eczema, exfoliative dermatitis, photosensitivity reactions,

		erythema multiforme,	
		alopecia, severe skin infections and soft-tissue complications in a varicella infection	eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders		Fluid retention; oedema. unexplained vaginal bleeding, blood in urine; cystitis; renal impairment or failure; polyuria, renal papillary or tubular necrosis,	Renal calculi or ureteral obstruction
		elevated uric acid concentrations in the blood, increase in serum creatinine, oedemas (particularly in patients with arterial hypertension or renal insufficiency), nephrotic syndrome, interstitial nephritis	

Pseudoephedrine hydrochloride

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Immune system disorders		Severe generalised hypersensitivity reactions, signs may be facial oedema, angioedema, dyspnoea, tachycardia, drop in blood pressure, anaphylactic shock	
Endocrine disorders			*A*ltered metabolism, including disturbances of glucose metabolism
Psychiatric disorders			Agitation, anxiety, abnormal behaviour, euphoric mood

Nervous system disorders	Nervousness, restlessness, insomnia	Giddiness, headache, sweating, muscular weakness, tremor, hallucinations, convulsion	Fear, confusion, irritability, psychotic states, tolerance with dependence may occur,
			haemorrhagic stroke, ischaemic stroke, somnolence
Eye disorders			Ischaemic optic neuropathy
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders		Tachycardia	Precordial pain, palpitations, hypertension and ventricular dysrhythmias may occur
Vascular disorders			Hypertension
Respiratory, thoracic and mediastinal disorders		Shortness of breath or troubled breathing,	Dyspnoea
		exacerbation of asthma or hypersensitivity reaction with bronchospasm	
Gastrointestinal disorders		Vomiting	Reduced appetite, thirst, ischaemic colitis
	Dry mouth, nausea		
Skin and subcutaneous tissue disorders		Rash, pruritus	Angioedema, severe skin reaction including acute generalised exanthematous pustulosis (AGEP), urticaria hyperhidrosis
Renal and urinary disorders		Difficult or painful urination	Urinary retention,
			dysuria

c) Description of selected adverse reactions

Cardiac disorders:

Many of the cardiovascular effects may occur secondary to NSAID-induced renal function impairment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Overdosage may result in nausea and vomiting.

Symptoms of sympathomimetic effect

CNS depression: e.g. sedation, apnoea, cyanosis, coma

CNS stimulation (which is more likely in children): e.g. insomnia, hallucinations, convulsions, tremor, mydriasis, anxiety, agitation.

Besides the symptoms already mentioned as undesirable effects (see section 4.8), the following symptoms can occur: hypertensive crisis, cardiac dysrhythmias, muscle weakness and tenseness, euphoria, excitement, thirst, chest pain, dizziness, tinnitus, ataxia, blurred

vision, hypotension, rhabdomyolysis, hypokalemia, palpitations, hypertension, and ischaemic bowel infarction.

Ibuprofen-related symptoms (in addition to the gastrointestinal and neurological symptoms already mentioned as undesirable effects)

Drowsiness, nystagmus, tinnitus, hypotension, loss of consciousness, abdominal pain, nausea, vomiting, lethargy, headache, renal failure, fulminant hepatic failure, bradycardia, tachycardia, atrial fibrillation.

In serious poisoning, metabolic acidosis may occur.

Treatment

Treatment is symptomatic and supportive.

No specific antidote is available.

Consider oral administration of activated charcoal if the patient presents within one hour of ingestion of a potentially toxic amount.

Electrolytes should be checked and ECG performed. In case of cardiovascular instability and/or symptomatic electrolyte imbalance, symptomatic treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 5.8 Preparation for the common cold including nasal decongestants and antihistaminics.

Pharmacotherapeutic group: Cough and cold preparations; other cold preparations.

ATC code: R05X

Mechanism of action

DECLOZIT has decongestive, analgesic and antipyretic properties.

Pseudoephedrine hydrochloride is a sympathomimetic medicine which, when administered systemically, acts as a nasal decongestant.

Ibuprofen is an NSAID belonging to the propionic acid class of medicines. It is an arylcarboxylic acid derivative which has analgesic, antipyretic and anti-inflammatory properties as well as a short-acting inhibitory effect on platelet function. All of these properties are related to its ability to inhibit prostaglandin synthesis.

DECLOZIT is a combination of a vasoconstrictor (pseudoephedrine hydrochloride) with an analgesic dose of an NSAID (ibuprofen).

5.2. Pharmacokinetic properties

Ibuprofen

Absorption

Peak serum levels are reached approximately 90 minutes after oral dosing.

With single oral dose administration, peak serum levels in adults, are proportional to the dose (C_{max} 17 ± 3,5 µg/mL for a 200 mg dose and 30,3 ± 4,7 µg/mL for a 400 mg dose).

Absorption of ibuprofen is delayed by food ingestion.

Distribution

Ibuprofen does not accumulate. It is 99 % bound to plasma proteins.

In the synovial fluid, ibuprofen is recovered at steady concentrations two to eight hours after dosing, with C_{max} in the synovial fluid being about one third of plasma C_{max}. After administration of a 400 mg ibuprofen dose every 6 hours in breastfeeding women, the amount of ibuprofen recovered in breast milk is less than 1 mg per 24 hours.

Biotransformation

Ibuprofen does not have any enzyme-inducing effect. It is 90 % metabolised and converted into inactive metabolites.

Elimination

Ibuprofen is mainly excreted via the urine. Ibuprofen is completely excreted within 24 hours, with 10 % eliminated unchanged and 90 % in the form of inactive metabolites, mainly glucurono-conjugates.

Elimination half-life is approximately 2 hours.

Special populations

The pharmacokinetic parameters of ibuprofen are only slightly modified in the elderly, in renal failure patients and in patients with hepatic insufficiency. The alterations observed do not require dosage adjustment.

Pseudoephedrine hydrochloride

When administered by oral route, pseudoephedrine is excreted mainly via the kidney in unchanged form (70 % to 90 %).

Elimination half-life depends on urinary pH.

Urine alkalinisation results in an enhanced increase in tubular reabsorption, and consequently the prolongation of the elimination half-life of pseudoephedrine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Colloidal anhydrous silica, croscarmellose sodium, hypromellose, lactose monohydrate, maize starch, microcrystalline cellulose, pregelatinised maize starch, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, triacetin, red iron oxide, yellow iron oxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C, protected from light and air.

Keep blister in carton until required for use.

6.5. Nature and contents of container

12 or 24 tablets are packed in clear PVC/PVdC/silver aluminium foil blister strips, or clear PVC/Aclar/silver aluminium foil blister strips. Each blister strip contains 12 tablets. Blister strips are packed in an outer cardboard carton.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

56/5.8/0390

9. DATE OF FIRST AUTHORISATION

17 September 2024

10. DATE OF REVISION OF TEXT

17 September 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

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