SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Clarinase Repetabs
Prolonged Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg loratadine and 120 mg pseudoephedrine sulphate.
Excipients with known effect: The quantities of sucrose and lactose monohydrate in each prolonged-release tablet are 173.23 mg and 156.80 mg respectively.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Round, biconvex, lustrous, white, coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarinase Repetabs is indicated for the relief of symptoms of seasonal allergic rhinitis when both the antihistaminic properties and the nasal decongestant activity are desired.

4.2 Posology and method of administration

Posology

Adults and children 12 years of age and over:

One **Clarinase Repetabs** tablet twice daily with a glass of water.
The duration of treatment should be kept as short as possible and should not be continued after the symptoms have disappeared. It is advisable to limit treatment to about 10 days, as during chronic administration the activity of pseudoephedrine may diminish. After improvement of the congestive condition of the mucosae of the upper airway, treatment may be maintained with loratadine alone, if necessary.

Paediatric population

The safety and efficacy of *Clarinase Repetabs* in children below the age of 12 years have not been established. No data are available. Clarinase Repetabs are not recommended for use in children below the age of 12 years.

Elderly patients

The combination product should not be administered to patients above 60 years of age. Patients 60 years or older are more likely to experience adverse reactions to sympathomimetic medications (see section 4.4).

Patients with renal or hepatic impairment

The combination product should not be used in patients with impaired renal function, renal tubular acidosis or impaired hepatic function (see section 4.4).

Method of administration

Oral use. The tablet must be swallowed entirely (without crushing, breaking or chewing it). The tablet may be taken without regard to mealtime.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to adrenergic medicinal products.
As Clarinase Repetabs contains pseudoephedrine, it is also contraindicated in patients who are receiving irreversible monoamine oxidase (MAO) inhibitor therapy or during the 2 weeks following the stopping of such treatment, and in patients with:
- narrow-angle glaucoma
- urinary retention
- cardiovascular diseases such as ischaemic heart disease, tachyarrhythmia and severe hypertension

- hyperthyroidism
- a history of haemorhagic stroke or with risk factors which could increase the risk of haemorhagic stroke. This is due to the alpha-mimetic activity of pseudoephedrine, in combination with other vasoconstrictors such as bromocriptine, pergolide, lisuride, cabergoline, ergotamine, dihydroergotamine or any other decongestant medication used as a nasal decongestant, either by oral route or by nasal route (such as phenylpropanolamine, phenylephrine, ephedrine, oxymetazoline, naphazoline).
- Severe acute or chronic kidney disease or renal failure.
- Severe hypertension or uncontrolled hypertension.

4.4 Special warnings and precautions for use

Do not exceed the recommended dosage and the duration of treatment (see section 4.2).
Patients of 60 years or older are more likely to experience adverse reactions to sympathomimetic medications. The safety and efficacy of the combination have not been established in this population, and there are insufficient data to give adequate dose recommendations. The combination product should not be used in patients above 60 years of age.
Renal or hepatic impairment: The safety and efficacy of the combination have not been established in patients with impaired renal or hepatic function, and there are insufficient data to give adequate dose recommendations. The combination product should not be used in patients with impaired renal function, renal tubular acidosis or impaired hepatic function.
Patients should be informed that the treatment should be discontinued in case of hypertension, tachycardia, palpitations or cardiac arrhythmias, nausea or any other neurologic sign (such as headache or increased headache).
Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines. These effects may be more likely to occur in children, the elderly, or in cases of overdose (see section 4.9).

Caution should be exercised in patients receiving digitalis, those with cardiac arrhythmias, hypertension, a history of myocardial infarction, diabetes mellitus, bladder neck obstruction, or positive anamnesis of bronchospasm.
Use with caution in patients with stenosing peptic ulcer, pyloroduodenal obstruction and obstruction of the vesical cervix.
Oral administration of pseudoephedrine at the recommended dose can cause other sympathomimetic effects, such as increased blood pressure, tachycardia or manifestations of central nervous system excitation.
Concomitant administration of sympathomimetics and reversible MAO inhibitors (such as linezolide [non-selective] and moclobemide [MAO-A selective] are not recommended.
Caution should also be exercised in patients being treated with other sympathomimetics, including decongestants, anorexogenics or amphetamine-type psychostimulants, antihypertensive agents, tricyclic antidepressants and other antihistamines.
Caution should be exercised in patients who are currently being treated with ergot alkaloid vasoconstrictors.
As with other CNS stimulants, pseudoephedrine sulphate carries the risk of abuse. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. Depression may follow rapid withdrawal.
Perioperative acute hypertension can occur if volatile halogenated anaesthetics are used during treatment with indirect sympathomimetic agents. Therefore, if surgery is scheduled, it is preferable to discontinue treatment 24 hours before anaesthesia.
Athletes should be informed that treatment with pseudoephedrine could lead to positive dope-tests.
This medicinal product contains lactose and sucrose; thus patients with rare hereditary problems of fructose, galactose intolerance, total lactase deficiency, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.
The administration of **Clarinase Repetabs** should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.

Severe Skin reactions

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. 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 localised 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 *Clarinase Repetabs* should be discontinued and appropriate measures taken if needed.

Ischaemic colitis
Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine 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. Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)
Cases of PRES and RCVS have been reported with the use of pseudoephedrine containing products (see section 4.8). The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3).
Pseudoephedrine should be discontinued and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment.

4.5 Interaction with other medicinal products and other forms of interaction
When administered concomitantly with alcohol, loratadine has no potentiating effects as measured by psychomotor performance studies.

CYP3A4 and CYP2D6 inhibitors have been shown to increase loratadine and desloratadine exposure. However, due to the wide therapeutic index of loratadine, no clinically relevant interactions are expected and none were observed with co-administration of erythromycin, ketoconazole and cimetidine in the conducted clinical trials (see section 5.2).
Concurrent administration of monoamine oxidase inhibitors (reversible or irreversible) and sympathomimetic medicines can cause critical hypertension reactions.
Sympathomimetic medicines may reduce the effect of antihypertensive medicines.
The following combinations are not recommended:
Bromocriptine, cabergoline, lisuride, pergolide: risk of vasoconstriction and increase in blood pressure.
Dihydroergotamine, ergotamine, methylergometrine: risk of vasoconstriction and increase in blood pressure.
Reversible and irreversible MAO inhibitor(s): risk of vasoconstriction and increase in blood pressure.
Other vasoconstrictors used as nasal decongestant, by oral or nasal route, (such as phenylpropanolamine, phenylephrine, ephedrine, oxymetazoline, naphazoline): risk of vasoconstriction.

<u>Paediatric population</u>
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
Pregnancy
Neither loratadine nor the combination of loratadine and pseudoephedrine were teratogenic in animal studies. The safe use of Clarinase Repetabs during pregnancy has not been established; however experience from a large number of exposed pregnancies in humans does not reveal any increase in the frequency of malformations as compared to the incidence in the general population.
Because animal reproduction studies are not always predictive of human response, and due to the vasoconstrictive properties of pseudoephedrine, Clarinase Repetabs should not be used during pregnancy.

Breast-feeding
Physico-chemical data suggest excretion of loratadine and pseudoephedrine/metabolites in human milk. Decreased milk production in nursing mothers has been reported with pseudoephedrine. A risk to the newborns/infants cannot be excluded. Therefore Clarinase Repetabs should not be used during breast-feeding.

Fertility
There are no data available on male and female fertility.

4.7 Effects on ability to drive and use machines

Clarinase Repetabs has no or negligible influence on the ability to drive and use machines. In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, some people very rarely experience drowsiness, which may affect their ability to drive or use machines.
It is not expected that pseudoephedrine sulphate impairs psychomotor performance.

4.8 Undesirable effects

Tabulated list of adverse reactions
The following adverse reactions reported during clinical trials in excess of placebo for 5 mg/120 mg prolonged-release tablets are listed in the following table by System Organ Class. Frequencies are defined as very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (> 1/10,000, < 1/1000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

System Organ Class	Frequency Category	Adverse Reactions
Metabolism and nutrition disorders	Common	Thirst
Psychiatric disorders	Common	Nervousness, somnolence, depression, agitation, anorexia
	Very Common	Insomnia
Nervous system disorders	Uncommon	Confusion, tremor, increased sweating, hot flushes, taste perversion
	Common	Dizziness
Eye disorders	Uncommon	Abnormal lacrimation
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Palpitation
	Common	Tachycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Epistaxis
	Common	Pharyngitis, rhinitis
Gastrointestinal disorders	Common	Constipation, nausea, dry mouth

Skin and subcutaneous tissue disorders	Uncommon	Pruritus
Renal and urinary disorders	Uncommon	Micturition frequency and disorder
General disorders and administration site conditions	Common	Headache, fatigue

Other adverse reactions reported during the post-marketing period are listed in the following table.

System Organ Class	Frequency Category	Adverse Reactions
Immune system disorders	Very rare	Hypersensitivity reactions (such as anaphylaxis, rash, urticaria, and angioedema)
Nervous system disorders	Very rare	Vertigo, convulsions
	Not known	Posterior reversible encephalopathy syndrome (PRES) (see section 4.4) Reversible cerebral vasoconstriction syndrome (RCVS) (see section 4.4)
Cardiac disorders	Very rare	Cardiac arrhythmias
Vascular disorders	Very rare	Hypertension
Respiratory, thoracic and mediastinal disorders	Very rare	Cough, bronchospasm
Hepatobiliary disorders	Very rare	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Very rare	Alopecia
	Unknown	Severe skin reactions, including acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Very rare	Urinary retention
Gastrointestinal disorders	Unknown	Ischaemic colitis
Investigations	Not known	Weight increased
Eye disorders	Unknown	Ischaemic optic neuropathy

Other adverse reactions that were only reported for loratadine in clinical trials and during the post-marketing period include increased appetite, rash and gastritis.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms of overdose
Symptoms of overdose are mostly of a sympathomimetic nature, except for slight sedation that can be caused by loratadine at doses many times higher than the recommended dose. Symptoms may vary from CNS depression (sedation, apnoea, diminished mental alertness, cyanosis, coma, cardiovascular collapse) to CNS stimulation (insomnia, hallucination, tremors, convulsions) with possible fatal outcome. Other

symptoms may include: headache, anxiety, micturition difficulty, muscle weakness and tenseness, euphoria, excitement, respiratory failure, cardiac arrhythmias, tachycardia, palpitations, thirst, perspiration, nausea, vomiting, precordial pain, dizziness, tinnitus, ataxia, blurred vision and hypertension or hypotension. CNS stimulation is particularly likely in children, as are atropine-like symptoms (dry mouth, fixed and dilated pupils, flushing, hyperthermia, and gastrointestinal symptoms). Some patients may present with a toxic psychosis with delusions and hallucinations.

Management of overdose

In the event of overdosage, start symptomatic and supportive treatment immediately and maintain it for as long as necessary. Adsorption of active substance remaining in the stomach may be attempted by administration of active charcoal suspended in water. Perform gastric lavage with physiologic saline solution, particularly in children. In adults, tap water can be used. Remove as much as possible of the amount administered before the next instillation. Loratadine is not removed by haemodialysis and it is not known if loratadine is eliminated by peritoneal dialysis. After emergency treatment, continue to monitor the patient medically.

Treatment of the pseudoephedrine overdosage is symptomatic and supportive. Stimulants (analeptics) must not be used. Hypertension can be controlled with an alpha-blocking agent and tachycardia with a beta-blocking agent. Short acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or hypothermia blanket. Apnoea is treated with respiratory assistance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines – H_1 antagonist, ATC code: R06A X13.
Pharmacotherapeutic group: Nasal decongestants for systemic use group, ATC code: R01BA52.

Mechanism of action

Loratadine is a tricyclic antihistamine with selective, peripheral H_1-receptor activity.
Pseudoephedrine sulphate (d-isoephedrine sulphate) is a sympathomimetic agent with mostly α-mimetic activity in comparison with the β-activity. Pseudoephedrine sulphate provides a nasal decongestant effect after oral administration due to its vasoconstrictive action. It has an indirect sympathomimetic effect due primarily to the release of adrenergic mediators from the post-ganglionic nerve endings.

Pharmacodynamic effects

The pharmacodynamics of Clarinase Repetabs tablets are directly related to that of its components.
Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.
During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.
Loratadine has no significant H_2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

5.2 Pharmacokinetic properties

Loratadine

Absorption

Loratadine is rapidly and well-absorbed. Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect. The bioavailability of loratadine and of the active metabolite are dose proportional.
Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).

Distribution
Loratadine is highly bound (97 % to 99 %) and its active major metabolite desloratadine (DL) moderately bound (73 % to 76 %) to plasma proteins.
In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively.

Biotransformation
After oral administration, loratadine undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desloratadine (DL) is pharmacologically active and responsible for a large part of the clinical effect. Loratadine and DL achieve maximum plasma concentrations (T_{max}) between 1–1.5 hours and 1.5–3.7 hours after administration, respectively.

Elimination
Approximately 40 % of the dose is excreted in the urine and 42 % in the faeces over a 10 day period and that, mainly in the form of conjugated metabolites. Approximately 27 % of the dose is eliminated in the urine during the first 24 hours. Less than 1 % of the active substance is excreted unchanged in active form, as loratadine or DL.
The mean elimination half-lives are 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the active metabolite.

Renal impairment
In patients with chronic renal impairment, both the area under the curve (AUC) and peak plasma levels (C_{max}) increased for loratadine and its active metabolite as compared to the AUCs and peak plasma levels (C_{max}) of patients with normal renal function. The mean elimination half-lives of loratadine and its active metabolite were not significantly different from those observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.

Hepatic impairment
In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (C_{max}) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and its metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Elderly
The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

<u>Pseudoephedrine sulphate</u>
Absorption
After oral administration, pseudoephedrine sulphate is rapidly and completely absorbed. Onset of action occurs within 30 minutes and a dose of 60 mg has a decongestive action lasting for 4 to 6 hours.
Food may increase the amount of loratadine absorbed, but without clinically significant results. This is not observed with pseudoephedrine.

Distribution
Pseudoephedrine is presumed to cross the placenta and the haematoencephalic barrier.
The active substance is excreted in breast milk of lactating women.

Biotransformation
Pseudoephedrine sulphate undergoes incomplete hepatic metabolism by N-demethylation to an inactive metabolite.

Elimination
Its elimination half-life in humans, at an approximate urinary pH of 6, ranges from 5 to 8 hours. The active substance and its metabolite are excreted in urine, 55-75 % of the administered dose is excreted

unchanged. The rate of excretion is accelerated and the duration of action decreased in acidic urine (pH5). In case of alkalinisation of the urine, a partial resorption takes place.

5.3 Preclinical safety data

Non-clinical data for loratadine reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Toxicity for the combination:
In acute and multiple-dose studies, the combination of loratadine/pseudoephedrine sulphate exhibited a low order of toxicity. The combination was not more toxic than their individual components, and observed effects were generally related to the pseudoephedrine component.
In reproductive toxicity studies of loratadine, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats at plasma levels (AUC) 10 times higher than those achieved with clinical doses.
During reproductive toxicity studies, the combination of loratadine/pseudoephedrine was not teratogenic when administered orally to rats at doses up to 150 mg/kg/day (30 times the proposed clinical dose) and rabbits at doses up to 120 mg/kg/day (24 times the proposed clinical dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Lactose monohydrate
Corn starch
Povidone
Magnesium stearate

Coating:
Sucrose
Calcium sulphate anhydrous
Calcium sulphate dihydrate
Talc
Gum rosin nelio
Acacia
Zein
Titanium dioxide
Oleic acid
Cellulose microcrystalline
Soap powder
Carnauba wax
White wax

Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C. Store in the original blister packaging in order to protect from moisture. Do not freeze.

6.5 Nature and contents of container
Blister strip consisting of a clear, transparent PVC-PCTFE film (PVC in contact with product) and a lidding of aluminium foil with vinyl heat seal coating. The blister strips are enclosed in cartons in pack sizes of 2, 4, 6, 10, 14, 20, 28, 30 and 50 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.8 Registration Holder and Importer

Bayer Israel Ltd.
36 Hacharash St.
Hod Hasharon 45240

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