Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mirtazapine Grindeks 15 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 15 mg mirtazapine.
Excipient with known effect:
Each orodispersible tablet contains 1.5 mg aspartame

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

Round, white to off-white, beveled edge tablet, embossed with '15' on one side. The size of tablet is 7.5 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mirtazapine Grindeks is indicated in adults for the treatment of episodes of major depression

4.2 Posology and method of administration

Posology

Adults
The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg.
Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no clinical effect within another 2-4 weeks, treatment should be discontinued.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are asymptomatic.
It is recommended to discontinue treatment gradually to avoid withdrawal symptoms (see section 4.4).

Elderly
The recommended dosage is the same as for adults. In the elderly an increase in dosing should be done under close supervision to ensure a satisfactory and safe therapeutic response.

Renal impairment
Mirtazapine clearance may be reduced in patients with moderate to severe renal impairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing mirtazapine to this category of patients (see section 4.4).

Hepatic impairment
Mirtazapine clearance may be reduced in patients with hepatic impairment. This should be taken into account when prescribing mirtazapine to this category of patients, especially with severe hepatic impairment as patients with severe hepatic impairment have not been investigated (see section 4.4).

Paediatric population
Mirtazapine should not be used in children and adolescents below 18 years of age since efficacy was not demonstrated in two short-term clinical trials (see section 5.1) and because of safety concerns (see sections 4.4, 4.8 and 5.1).

Method of administration

Mirtazapine has an elimination half-life of 20-40 hours and therefore mirtazapine is suitable for use once a day. It should be taken preferably as a single night-time dose before going to bed. Mirtazapine may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).
Tablets should be taken orally. The tablets will dissolve quickly and can be swallowed without water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant treatment with monoamine oxidase inhibitors (MAOI) (see section 4.5).

4.4 Special warnings and precautions for use

Paediatric population
Mirtazapine should not be used in the treatment of children and adolescents under 18 years of age. In clinical trials, suicide related behaviour (suicide attempts and suicidal thoughts) and hostility (mainly aggression, oppositional behaviour and anger) occurred more frequently in children and adolescents treated with antidepressants than in those treated with placebo. If, based of clinical needs, a decision to treat a patient under 18 years of age is nevertheless taken, the patient should be closely monitored for possible suicidal symptoms. In addition, data on long-term safety in children and adolescents concerning growth and maturation as well as cognitive and behavioural development are lacking.

Suicide/suicidal thoughts or clinical deterioration
Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide. This risk persists until significant improvement occurs. Since improvement may not occur during the first weeks of treatment, or occur even later, the patient should be closely monitored until improvement occurs. It is a general clinical experience that suicide risk may increase during the early improvement phases.

Patients with a history of suicide-related events, or patients with significant degree of suicidal thoughts before starting treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should be carefully monitored during treatment. A meta-analysis based on placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour during treatment with antidepressants compared to placebo in patients younger than 25 years of age.

Patients treated with antidepressants, and especially those at high risk of suicidal behaviour, should be closely monitored in the early phases of treatment and in case of dose changes. Patients (and caregivers) should be advised to be alert for signs of clinical deterioration, suicidal behaviour/thoughts, or other behavioural changes and to seek immediate medical attention if such signs occur.

With regards to suicide risk, especially at the beginning of treatment, only the minimum possible number of Mirtazapine Grindeks orodispersible tablets should be prescribed, in accordance with good patient management, in order to reduce the risk of overdose.

Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with mirtazapine. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with mirtazapine. In the post-marketing monitoring with mirtazapine, agranulocytosis has been reported in very rare cases, mostly reversible but in some cases fatal. The fatal cases have mainly concerned patients over 65 years of age. Therefore, the physician should pay attention to symptoms such as fever, sore throat, stomatitis, or other signs of infection; if such symptoms occur, treatment should be discontinued, and blood counts examined.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme, which can be life-threatening or fatal, have been reported in association with mirtazapine treatment.
If signs and symptoms suggesting these reactions occur, mirtazapine should be discontinued immediately.
If the patient has developed any of these reactions when using mirtazapine, the patient must never be treated with mirtazapine thereafter.

Jaundice
Treatment should be discontinued if jaundice occurs.

Conditions requiring monitoring
Careful dosing and regular and frequent check-ups are necessary in patients with:

- Epilepsy and organic brain syndrome: Although clinical experience indicates that epileptic seizures are rare in treatment with mirtazapine, mirtazapine, like other antidepressants, should be initiated with caution in patients with a history of seizures. Treatment should be discontinued if a patient experiences seizures or in the event of an increase in the frequency of seizures.
- Hepatic impairment: After a single oral dose of 15 mg mirtazapine, the clearance of mirtazapine decreased by approximately 35% in patients with mild to moderate liver function impairment compared to patients with normal liver function. The mean concentration of mirtazapine in plasma was elevated by approximately 55%.
- Renal impairment: After a single oral dose of 15 mg mirtazapine in patients with moderate (creatinine clearance <40 ml/min) or severe (creatinine clearance ≤10 ml/min) renal impairment, clearance of mirtazapine was 30% and 50% decreased, respectively, compared to healthy individuals. The average plasma concentration of mirtazapine was about 55% and 115% increased, respectively. No significant differences were found in patients with mild renal impairment (creatinine clearance <80 ml/min) compared to the control group.
- Cardiac disease such as conduction disorders, angina pectoris and recent infarction, where usual precautions should be taken. and concomitant medicines administered carefully.
- Low blood pressure.
- Diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and careful monitoring is recommended.

Like with other antidepressants, the following should be taken into account:

- Worsening of psychotic symptoms may occur when antidepressants are administered to patients with schizophrenia or other psychotic disorders; paranoid thoughts may be intensified.
- When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued if a patient is entering a manic phase.
- Although mirtazapine is not addictive, post-marketing experience shows that abrupt discontinuation after long-term treatment can sometimes cause withdrawal symptoms. The majority of withdrawal symptoms are mild and transient. Among the withdrawal symptoms that have been reported, dizziness, agitation, anxiety, headache and nausea are the ones reported most frequently. Although they have been reported as withdrawal symptoms, one should be aware that these symptoms may be related to the underlying disease. As advised in section 4.2, it is recommended to discontinue mirtazapine gradually.
- Caution should be exercised in patients with micturition problems such as prostatic hypertrophy and in patients with acute narrow-angle glaucoma and increased intraocular pressure (although there is little risk of problems with mirtazapine as the anticholinergic activity is low).
- Akathisia/psychomotor restlessness: The use of antidepressants has been associated with the development of akathisia, which is characterized by an unpleasant or disturbing restlessness and the need to move frequently along with difficulty sitting or standing still. It most often occurs in the first weeks of treatment. In patients who develop these symptoms, an increase in dose can be harmful.
- Cases of QT prolongation, *torsade de pointes,* ventricular tachycardia, and sudden death have been reported following the marketing authorization of mirtazapine. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc prolonging medicinal products (see section 4.5 and section 4.9). Caution should be exercised when mirtazapine is prescribed to patients with known cardiovascular disease or heredity for QT prolongation, and with concomitant use of other medicinal products known to prolong the QT interval.

Hyponatremia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported in very rare cases with the use of mirtazapine. Caution should therefore be exercised in patients at increased risk, such as elderly patients or patients who are being treated concomitantly with medicines known to cause hyponatraemia.

Serotonin Syndrome
Interactions with serotonergic active substances: serotonin syndrome may occur when a selective serotonin reuptake inhibitor

(SSRI) is administered in combination with other serotonergic medicinal products (see section 4.5). Symptoms of serotonin syndrome can be hyperthermia, rigidity, myoclonus, autonomic disorders with possible rapid changes in vital signs, changes in mental status such as confusion, irritability and extreme agitation that can progress into delirium and coma. Caution should be exercised and a close clinical monitoring is required when these active substances are combined with mirtazapine. Treatment with mirtazapine should be discontinued if such events occur and supportive symptomatic treatment should be initiated. Post marketing experience shows that serotonin syndrome is rare in patients treated with mirtazapine alone (see section 4.8).

Elderly
Elderly patients are often more susceptible, especially with respect to the undesirable effects of antidepressant medicines. During clinical studies with mirtazapine, side effects have not been reported more frequently in elderly patients than in other age groups.

Aspartame
Each 15 mg orodispersible tablet contains 1.5 mg aspartame.

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

- Mirtazapine should not be given at the same time as MAO inhibitors or within two weeks of stopping treatment with MAO inhibitors. Conversely, approximately two weeks should pass before patients treated with mirtazapine can be treated with MAO inhibitors (see section 4.3).

- Similar to SSRIs, co-administration of other serotonergic substances (L-tryptophan, triptans, tramadol, linezolid, methylene blue, SSRIs, venlafaxine, lithium and preparations with St. John's Wort – *Hypericum perforatum*) may lead to serotonin associated effects (serotonin syndrome, see section 4.4). Caution should be exercised, and close clinical monitoring is required when these active substances are combined with mirtazapine.

- Mirtazapine may potentiate the sedating properties of benzodiazepines and other sedatives (most antipsychotics, antihistamine H1 antagonists, opioids). Caution should therefore be exercised when these medicinal products are prescribed concomitantly with mirtazapine.
- Mirtazapine may increase the central nervous system depressant effect of alcohol. Patients should therefore be advised to avoid taking alcoholic beverages at the same time.
- Mirtazapine at doses of 30 mg daily produced a small but statistically significant increase in international normalized ratio (INR) in patients treated with warfarin. Since a more pronounced effect of mirtazapine cannot be ruled out at higher doses, it is advisable to monitor INR in case of concomitant therapy with warfarin and mirtazapine.
- The risk of QT prolongation and/or ventricular arrhythmias (e.g. *torsade de pointes*) may increase with concomitant use of medicinal products that prolong the QTc interval (e.g. certain antipsychotic medicines and antibiotics).

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4-inducers, increased the clearance of mirtazapine twofold, resulting in a decrease in the mean plasma concentration of mirtazapine by 60% and 45%, respectively. When carbamazepine or another inducer of hepatic metabolism (e.g. rifampicin) given concomitantly with mirtazapine, it may be necessary to increase the dose of mirtazapine. If treatment with such medicinal product is discontinued, it may be necessary to lower the dose of mirtazapine.
- Co-administration of a potent CYP3A4 inhibitor, ketoconazole increased peak plasma levels and AUC of mirtazapine by approximately 40% and 50%, respectively.
- When cimetidine (a weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is given simultaneously with mirtazapine, the mean plasma concentration of mirtazapine may increase by more than 50%. Caution should be exercised, and the dose may need to be reduced if mirtazapine is given at the same time as a potent inhibitor of CYP3A4, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies have not shown any relevant pharmacokinetic effects with concomitant treatment with mirtazapine and paroxetine, amitriptyline, risperidone or lithium.

Paediatric population
Interaction studies have only been conducted in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited data from the treatment of pregnant women with mirtazapine indicate no increased risk of congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance, however, reproductive toxicity has been observed (see section 5.3).

Caution should be exercised when prescribing to pregnant women. If mirtazapine is used until, or shortly before birth, postnatal follow-up of the new-born is recommended to account for possible withdrawal symptoms.

Epidemiological data suggest that the use of SSRIs in pregnancy, especially at the end of pregnancy, may increase the risk of persistent pulmonary hypertension in the new-born (PPHN). Although no studies have investigated the relationship between PPHN and mirtazapine treatment, the potential risk cannot be ruled out when taking into account the mechanism of action (increase in serotonin concentration).

Breast-feeding
Animal studies and limited human data have shown that mirtazapine is excreted in breast milk in very small amounts. The decision to continue or stop breastfeeding and to continue or stop treatment with mirtazapine, respectively, must be made taking into account the benefits of breastfeeding for the baby and the benefits of treatment with mirtazapine for the woman.

Fertility
Non-clinical reproductive toxicity studies in animals showed no effect on fertility.

4.7 Effects on ability to drive and use machines

Mirtazapine has minor or moderate influence on the ability to drive and use machines. Mirtazapine may impair concentration and responsiveness (especially at the beginning of treatment). Patients should avoid dangerous situations that require good concentration and alertness, such as driving or operating machines, at any time when affected.

4.8 Undesirable effects

Depressed patients display a number of symptoms that may be associated with the disease itself. It can therefore be difficult to ascertain which symptoms are due to the disease itself and which are a result of the treatment with mirtazapine.

Summary of the safety profile
The most common reports of adverse reactions in the randomized placebo-controlled clinical trials (see below), which occurred in more than 5% of patients treated with mirtazapine are somnolance, sedation, dry mouth, weight gain, increased appetite, dizziness and fatigue.
Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme have been reported in association with mirtazapine treatment (see section 4.4).

Tabulated list of adverse reactions
All randomized placebo-controlled trials in patients (including indications other than major depression) have been used to evaluate mirtazapine side effects. The meta-analysis includes 20 trials with a planned treatment duration of up to 12 weeks with 1501 patients (134 patient years) receiving mirtazapine doses of up to 60 mg and 850 patients (79 patient years) receiving placebo. In order to maintain the comparison with placebo, follow-up studies of these have been excluded.

Table 1 shows the incidence of different categories of adverse reactions that occurred statistically significantly more frequently with mirtazapine than with placebo in the clinical studies, with adverse reactions from spontaneous reporting added. The frequency of adverse reactions from spontaneous reporting is based on the reporting of these in the clinical trials. The frequency of adverse reactions from spontaneous reporting where no cases of mirtazapine were reported in the randomized placebo-controlled trials has been classified as 'not known'.

Table 1. Adverse reactions of mirtazapine

System organ class	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)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					• Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia thrombocytopenia) • Eosinophilia
Endocrine disorders					• Inappropriate antidiuretic hormone secretion • Hyperprolactinemia (and related symptoms – galactorrhoea and gynecomastia)
Metabolism and nutrition disorders	• Weight gain[1] • Increased appetite[1]				• Hyponatraemia
Psychiatric disorders		• Abnormal dreams • Confusion • Anxiety[2, 5] • Insomnia[3, 5]	• Nightmares[2] • Mania • Agitation[2] • Hallucinations • Psychomotor restlessness (incl. akathi	• Aggression	• Suicidal thoughts[6] • Suicidal behaviour[6] • Somnambulism

			sia, hyperkinesia)		
Nervous system disorders	• Somnolence[1,4] • Sedation[1, 4] • Headache[2]	• Lethargy[1] • Dizziness • Tremor • Amnesia	• Paraesthesia[2] • Restless legs • Syncope	• Myoclonus	• Convulsions (seizures) • Serotonin syndrome • Oral paraesthesia • Dysarthria
Vascular disorders		• Orthostatic hypotension	• Hypotension[2]		
Gastrointestinal disorders	• Dry mouth	• Nausea[3] • Diarrhoea[2] • Vomiting[2] • Constipation[1]	• Oral hypoesthesia	• Pancreatitis	• Oedema of the mouth • Increased salivation
Hepatobiliary disorders				• Elevated transaminases in serum	
Skin and subcutaneous tissue disorders		• Exanthema[2]			• Stevens-Johnson syndrome • Dermatitis bullous • Erythema multiforme • Toxic epidermal necrolysis • Drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders		• Arthralgia • Myalgia • Back pain[1]			• Rhabdomyolysis
Renal and urinary disorders					• Urinary retention
Reproductive system and breast disorders					• Priapism
General disorders and administration site conditions		• Oedema peripheral[1] • Fatigue			• Oedema, generalised • Oedema, localised
Investigations					• Increased amount of creatine kinase

[1] In clinical trials, these adverse reactions have occurred statistically significantly more frequently with mirtazapine than with placebo.
[2] In clinical trials, these adverse reactions have occurred more frequently with placebo than with mirtazapine, but not statistically significantly more frequently.
[3] In clinical trials, these adverse reactions have occurred statistically significantly more frequently with placebo than with mirtazapine.
[4] Note. Dose reduction generally does not lead to less somnolence/sedation but can jeopardize the antidepressant effect.
[5] When treated with antidepressants in general, anxiety and insomnia (which can also be symptoms of depression) can develop or become aggravated. During treatment with mirtazapine, the development of aggravation or anxiety and insomnia has been reported.
[6] Cases of suicidal ideation and suicidal behaviour have been reported during treatment with mirtazapine or shortly after treatment has ended (see section 4.4).
*In most cases patients recovered after withdrawal.

Laboratory evaluations in the clinical trials have observed transient increases in transaminases and gamma-glutamyltransferase (however, associated adverse reactions have not been reported statistically significantly more frequently with mirtazapine than with placebo).

Paediatric population
The following common adverse reactions were observed in clinical trials in children: weight gain, urticaria and hypertriglyceridaemia (see also section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Present experience concerning overdose with mirtazapine alone indicates that the symptoms are usually mild. The influence of the central nervous system with confusion and prolonged sedation has been reported along with tachycardia and mild hyper- or hypotension. However, there is a risk of more serious outcomes (including fatalities) at doses significantly higher than the therapeutic ones, especially in the case of combined overdose. In these cases, QT prolongation and *torsade de pointes* have also been reported.

In case of overdose, symptomatic treatment and support of vital functions should be given. ECG monitoring should take place. Activated charcoal or gastric lavage should also be considered.

Paediatric population
The appropriate measures described for adults should be taken in case of overdose in paediatric patients.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, Other antidepressants, ATC code: N06AX11

Mechanism of action/pharmacodynamic effects
Mirtazapine is a centrally acting presynaptic α2 antagonist, which increases the central noradrenergic and serotonergic neurotransmission. The increase in serotonergic neurotransmission is specifically mediated via 5-HT1 receptors because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are persumed to contribute to the antidepressant effect. S(+) the enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.

Clinical efficacy and safety
The histamine H_1-antagonistic effect of mirtazapine is linked to the sedative properties. Mirtazapine practically lacks anticholinergic activity and, in therapeutic doses, has only limited effect (e.g., orthostatic hypotension) on the cardiovascular system.

The effect of mirtazapine on QTc intervals was evaluated in a randomized placebo- and moxifloxacin-controlled clinical trial in 54 healthy volunteers treated with a regular dose of 45 mg and a supratherapeutic dose of 75 mg. Linear E-max modelling suggested that prolongation of QTc intervals remained below the clinically significant prolongation threshold (see section 4.4).

Paediatric population
Two randomized, double-blind, placebo-controlled trials in children between 7 and 18 years of age with major depressive disorder (n=259) with an adapted dose during the first 4 weeks (15-45 mg mirtazapine) followed by a fixed dose (15, 30 or 45 mg mirtazapine) for an additional 4 weeks, failed to demonstrate significant differences between mirtazapine and placebo for the primary and all secondary endpoints. Significant weight gain (≥7%) was observed in 48.8% of mirtazapine-treated subjects compared to 5.7% in the placebo arm. Urticaria (11.8% vs 6.8%) and hypertriglyceridemia (2.9% vs 0%) were also common.

5.2 Pharmacokinetic properties

Absorption
After oral administration of mirtazapine tablets, the active substance, mirtazapine, is rapidly and well absorbed (bioavailability ≈50%), reaching the maximum plasma concentration after about 2 hours. Food intake does not affect the pharmacokinetics of mirtazapine.

Distribution
The binding of mirtazapine to plasma proteins is about 85%.

Biotransformation
The main pathways of the biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that the cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, while CYP3A4 is considered responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent substance.

Elimination
Mirtazapine is extensively metabolized and eliminated in urine and faeces within a few days. The average half-life of elimination is 20-40 hours. Longer half-lives, up to 65 hours, have sometimes been observed and shorter half-lives have been seen in younger men. The elimination half-life is sufficient to recommend dosing once a day. Steady-state levels are reached after 3-4 days, and after that no further accumulation occurs.

Linearity/non-linearity
Mirtazapine has linear pharmacokinetics within the recommended dose range.

Special populations
Clearance of mirtazapine may decrease in patients with impaired renal or hepatic function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In reproduction studies in rats and rabbits, no teratogenic effects were observed. At two-fold systemic exposure compared to maximum human therapeutic exposure, there was an increase in post-implantation loss, decrease in the pup birth weights, and reduction in pup survival during the first three days of lactation in rats.

Mirtazapine was not genotoxic in a series of studies with tests for gene mutation, chromosomal and DNA damage. Thyroid tumours in rats as well as hepatocellular neoplasm in mice seen in carcinogenicity studies are considered to be species-specific, non-genotoxic responses associated with long-term treatment with high doses of liver enzyme inducers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Cellulose, microcrystalline
Crospovidone
Silica, colloidal anhydrous
Hydroxypropylcellulose, low-substituted
Aspartame (E951)
Orange flavour
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

oPA/Alu/PVC//Alu blisters containing 28, 30, 50, 56, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

AS Grindeks
Krustpils Iela 53
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA22992/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th August 2025

10 DATE OF REVISION OF THE TEXT