

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Sabrilan 500 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg vigabatrin

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

White to off-white, oval, biconvex tablets with a score line on one side and "SABRIL" engraved on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Visual field defects (VFD) have been reported in patients receiving vigabatrin with a high prevalence (about 1/3 of patients). Frequencies found in an open- clinical study are presented in section 5.1. The onset is usually after months to years of vigabatrin therapy. The degree of visual field restriction may be severe. Most of the patients with perimetry-confirmed defects have been asymptomatic. Hence, this undesirable effect can only be reliably detected by systematic perimetry which is usually possible only in patients with a developmental age of more than 9 years. A specifically developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test the presence of peripheral vision in children aged 3 years and above. At present this method has not been validated in the detection of vigabatrin-attributed visual field defects. Electroretinography may be useful but should be used only in adults who are unable to cooperate with perimetry or in the very young (see Visual Field Defects).

Available data suggests that visual field defects are irreversible even after discontinuation of vigabatrin. A deterioration of VFD after the treatment is discontinued cannot be excluded.

Therefore, vigabatrin should only be used after a careful assessment of the balance of benefits and risk compared with alternatives.

Vigabatrin is not recommended for use in patients with any pre-existing clinically significant visual field defect.

Patients should undergo systematic screening examination when starting vigabatrin and at regular intervals for detection of visual field defects and reduced visual acuity. Visual field testing and assessment of visual acuity should continue at 6-month intervals for the whole duration of treatment (see Visual Field Defects and Visual Acuity).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalization, that is where all other appropriate drug combinations have proven inadequate or have not been tolerated.

4.2 Posology and method of administration

Sabrilan treatment may only be initiated by a specialist in epileptology, neurology or paediatric neurology. Follow up should be arranged under supervision of a specialist in epileptology, neurology or paediatric neurology.

Posology

Sabrilan is intended for oral administration once or twice daily and may be taken before or after meals. The tablets should be swallowed with half a glass of water.

If there is no clinically significant improvement in epileptic symptoms following well-conducted initial treatment, Sabrilan should not be continued. Sabrilan should gradually be withdrawn under close medical supervision.

Tablets are not suitable for children under the age of 6 years, because of the risk of false passage.

Adults

Maximal efficacy is usually obtained with a daily dose of 2 to 3 g. A starting dose of 1 g daily should be added to the patient's current anti-epileptic drug regimen. The daily dose should then be increased in 0.5 g increments at weekly intervals depending on clinical response and tolerability. The maximum recommended dose is 3g/ day.

No direct correlation exists between the plasma concentrations and the efficacy. The duration of the effect of the drug is dependent on the rate of GABA-Transaminase resynthesis rather than plasma drug concentrations (see Section 5.1 and 5.2).

Children

The recommended starting dose in children is 40 mg/kg/day. Recommendations in relation to bodyweight for maintenance treatment are as follows:

<u>Bodyweight</u>	<u>Dosage</u>
10-15 kg	0.5-1 g/day
15-30 kg	1-1.5 g/day
30-50 kg	1.5-3 g/day
> 50 kg	2-3 g/day

The maximum recommended dose in each of these bodyweight categories must not be exceeded.

Elderly subjects and patients with renal insufficiency

Since vigabatrin is eliminated via the kidney, caution should be exercised when administering the drug to the elderly and more particularly in patients with creatinine clearance less than 60 ml/min. Adjustment of dose or frequency of administration must be considered. Such patients may respond to a lower maintenance dose. Patients should be monitored for undesirable effects such as sedation or confusion (see Sections 4.4 and 4.8).

4.3 Contraindications

Hypersensitivity to vigabatrin or to any of the excipients listed in section 6.1

4.4 Special Warnings and precautions for use

Sabrilan should not be instituted as monotherapy.

Visual Field Defects (VFD)

Based on available data, the usual pattern is a concentric constriction of the visual field of both eyes, which is generally more marked nasally than temporally. In the central visual field (within 30 degree of eccentricity), frequently an annular nasal defect is seen. However, the VFDs reported in patients receiving vigabatrin have ranged from mild to severe. Severe cases may be characterized by tunnel vision. Blindness was also reported in severe cases.

Most patients with perimetry confirmed defects had not previously spontaneously noticed any symptoms, even in cases where a severe defect was observed in perimetry.

Available evidence suggests that the VFD is irreversible even after discontinuation of vigabatrin. A deterioration of VFD after the treatment is discontinued cannot be excluded.

Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy have VFDs. Males may be at greater risk than females. Frequencies found in an open clinical study are presented in section 5.1. A possible association between the risk of visual field defects and the extent of vigabatrin exposure, both in terms of daily dose (from 1 gram to more than 3 grams) and in terms of duration of treatment (maximum during the first three years) has been shown in this study.

All patients should have ophthalmological consultation with visual field examination before the initiation of vigabatrin treatment.

Appropriate visual field testing (perimetry) by using a standardised static perimetry (Humphrey or Octopus) or kinetic perimetry (Goldmann) must be performed before treatment initiation and at six month intervals for the whole duration of treatment. Static perimetry is the preferred method for detecting vigabatrin associated visual field defect.

Electroretinography may be useful but should only be used in adults who are unable to cooperate with perimetry. Based on the available data the first oscillatory potential and 30 Hz flicker responses of the electroretinogram appear to be correlated with a vigabatrin associated VFD. These responses are delayed and reduced beyond the normal limits. Such changes have not been seen in vigabatrin treated patients without a

VFD. The patient and/or caregiver must be given a thorough description of the frequency and implications of the development of VFD during vigabatrin treatment. Patients should be instructed to report any new visual problems and symptoms which may be associated with visual field constriction. If visual symptoms develop, the patient should be referred to an ophthalmologist.

If a visual field constriction is observed during follow-up, consideration should be given to gradual discontinuation of vigabatrin. If the decision to continue treatment is made, consideration should be given to more frequent follow-up (perimetry) in order to detect progression or sight threatening defects.

Vigabatrin should not be used concomitantly with other retinotoxic drugs.

Paediatric population

Perimetry is seldom possible in children less than 9 years of developmental age. The risks of treatment must be very carefully weighed against possible benefit in children. Currently, there is no established method to diagnose or exclude visual field defects in children in whom a standardised perimetry cannot be performed. A specifically developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test the presence of peripheral vision in children aged 3 years and above. At present this method has not been validated in the detection of vigabatrin-attributed visual field defects. If the method reveals normal central visual field response but an absent peripheral response, benefit-risk of vigabatrin must be reviewed and consideration given to gradual discontinuation. The presence of peripheral vision does not exclude the possibility of developing VFD. Electroretinography may be useful but should be used only in children less than 3 years of age.

Visual acuity

The prevalence of reduced visual acuity in vigabatrin treated patients is unknown.

Retinal disorder, blurred vision, optic atrophy or optic neuritis may lead to decrease in visual acuity (see section 4.8). Visual acuity should be assessed during ophthalmological consultations, before initiation of vigabatrin treatment and at six-month intervals during treatment.

Neurological and psychiatric conditions

In view of the results of the animal safety studies (see section 5.3), it is recommended that patients treated with vigabatrin are closely observed for adverse effects on neurological function.

Rare reports of encephalopathic symptoms such as marked sedation, stupor and confusion in association with nonspecific slow wave activity on electroencephalogram have been described soon after the initiation of vigabatrin treatment. Risk factors for the development of these reactions include higher than recommended starting dose, faster dose escalation at higher steps than recommended, and renal failure. These events have been reversible following dose reduction or discontinuation of vigabatrin. (see section 4.8).

Cases of abnormal brain MRI findings have been reported, in particular in young infants treated for infantile spasms with high doses of vigabatrin. The clinical significance of these findings is currently unknown. Additionally, cases of intramyelinic oedema (IME) have been reported, particularly in infants treated for infantile spasms (see section 4.8 and 5.3). IME has been reported to be reversible following drug discontinuation, and it is therefore recommended to progressively discontinue vigabatrin when IME is observed.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with vigabatrin (see section 4.8). These phenomena may also be the consequence of an overdose, a decrease in plasma concentrations of concomitant antiepileptic treatment, or a paradoxical effect.

As with other antiepileptic drugs, abrupt withdrawal may lead to rebound seizures. If a patient is to be withdrawn from vigabatrin treatment, it is recommended that this is done by gradual dose reduction over a 2 to 4-week period.

Vigabatrin should be used with caution in patients with a history of psychosis, depression or behavioural problems. Psychiatric events (e.g., agitation, depression, abnormal thinking, paranoid reactions) have been reported during vigabatrin treatment. These events occurred in patients with and without a psychiatric history, and were usually reversible when vigabatrin doses were reduced or gradually discontinued.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised, placebo-controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this effect is not known and the available data do not exclude the possibility of an increased risk for vigabatrin.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

Older people and patients with renal impairment

Since vigabatrin is eliminated via the kidney, caution should be exercised in patients with a creatinine clearance of less than 60 ml/min and in older people. These patients should be monitored closely for undesirable effects such as sedation and confusion. (see section 4.2).

Interactions to be taken into account

The concomitant use of vigabatrin and clonazepam may exacerbate the sedative effect (see section 4.5). Need for concomitant use must be carefully assessed.

4.5 Interaction with other medicinal products and other forms of interaction

As vigabatrin is neither metabolised, nor protein bound and is not an inducer of hepatic cytochrome P450 drug-metabolising enzymes, interactions with other drugs are unlikely. However, during controlled clinical studies, a gradual reduction of 16-33% in the plasma concentration of phenytoin has been observed. The exact nature of this interaction is presently not understood, however, in the majority of cases it is unlikely to be of therapeutic significance.

The plasma concentrations of carbamazepine, phenobarbital and sodium valproate have also been monitored during controlled clinical trials and no clinically significant interactions have been detected.

Vigabatrin may lead to a decrease in measured plasma activity of alanine aminotransferase (ALT) and to a lesser extent, aspartate aminotransferase (AST). The magnitude of suppression for ALT has been reported to vary between 30% and 100%. Therefore, these liver tests may be quantitatively unreliable in patients taking vigabatrin. (see section 4.8).

Vigabatrin may increase the amount of amino acids in the urine possibly leading to a false positive test for certain rare genetic metabolic disorders (e.g., alpha aminoacidic aciduria).

The concomitant use of vigabatrin and clonazepam may exacerbate the sedative effect (see Section 4.4)

4.6. Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

In the offspring of women treated with antiepileptic medication, the prevalence of malformations is two to three times greater than in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Polytherapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible.

Specialist advice should be provided to all patients who could begin a pregnancy or who are in the fertile age. The need of antiepileptic treatment must be re-evaluated when a patient plans a pregnancy.

If a patient becomes pregnant, effective antiepileptic therapy should not be suddenly interrupted, since the aggravation of the illness may be detrimental to both the mother and the foetus.

Risk related to vigabatrin

Based on data on pregnancies exposed to vigabatrin, available from spontaneous reports, abnormal outcomes (congenital anomalies or spontaneous abortion) were reported in the offspring of mothers taking vigabatrin. No definite conclusion can be drawn as to whether vigabatrin produces an increased risk of malformation when taken during pregnancy because of limited data and the presence of concomitant antiepileptics.

Studies in animals have shown reproductive toxicity (see section 5.3).

Sabrilan should not be used during pregnancy unless the clinical condition of the woman requires treatment with vigabatrin.

There is limited amount of information on the possible occurrence of visual field defect in children who have been exposed to vigabatrin in utero.

Breast-feeding

Vigabatrin is excreted into human milk. There is insufficient information on the effects of vigabatrin in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Sabrilan therapy taking into account the benefit to breast-feeding for the child and the benefit therapy for the woman.

Fertility

Fertility studies in rats have shown no effect on male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

As a general rule, patients with uncontrolled epilepsy are not allowed to drive or handle potentially dangerous machinery. In view of the fact that drowsiness has been observed in clinical trials with Sabrilan, patients should be warned of this possibility at the start of treatment.

Visual field defects which can significantly affect the ability to drive and use machines have been frequently reported in association with Sabrilan. Patients should be evaluated for the presence of visual field defect (see also section 4.4). Special care should be taken by patients driving, operating machinery or performing any hazardous task.

4.8. Undesirable effects

Summary of the safety profile

Visual field defects ranging from mild to severe have been reported frequently in patients receiving vigabatrin. Severe cases are potentially disabling. The onset is usually after months to years of vigabatrin therapy. Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy develop visual field defects (see also section 4.4).

Approximately 50% of patients in controlled clinical studies have experienced undesirable effects during vigabatrin treatment. In adults, these were mostly central nervous system-related such as sedation, drowsiness, fatigue and impaired concentration. However, in children, excitation or agitation is frequent. The incidence of these undesirable effects is generally higher at the beginning of treatment and decreases with time.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency, including status epilepticus with vigabatrin. Patients with myoclonic seizures may be particularly liable to this effect. New-onset myoclonus and exacerbation of existing myoclonus may occur in rare cases.

Tabulated list of adverse reactions

Undesirable effects ranked under headings of frequency are listed below, using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very rare	Not known
<i>Blood and lymphatic system disorders</i>		anaemia				
<i>Psychiatric disorders*</i>		agitation, aggression, nervousness, depression, paranoid reaction insomnia .	hypomania, mania, psychotic disorder	suicide attempt	hallucination	
<i>Nervous system disorders</i>	somnolence	speech disorder, headache, dizziness, paraesthesia, disturbance in attention and memory impairment, mental impairment (thought disturbance), tremor	coordination abnormal (ataxia)	encephalopathy**	optic neuritis	Cases of brain MRI abnormalities have been reported, intramyelinic oedema (particularly in infants) (see sections 4.4 and 5.3).
<i>Eye disorders</i>	visual field defect	vision blurred, diplopia, nystagmus		retinal disorder (mainly peripheral)	optic atrophy	Reduced visual acuity
<i>Gastrointestinal disorders</i>		nausea, vomiting, abdominal pain				
<i>Hepato-biliary disorders</i>					hepatitis	
<i>Skin and subcutaneous tissue disorders</i>		alopecia.	rash	angioedema, urticaria		
<i>Musculoskeletal and connective tissue disorders</i>	arthralgia					
<i>General Disorders and administration site conditions</i>	fatigue	oedema, irritability				
<i>Investigations***</i>		weight increased				

*Psychiatric reactions have been reported during vigabatrin therapy. These reactions occurred in patients with and without a psychiatric history and were usually reversible when vigabatrin doses were reduced or gradually discontinued (see section 4.4). Depression was a common psychiatric reaction in clinical trials but seldom required discontinuation of vigabatrin.

**Rare reports of encephalopathic symptoms such as marked sedation, stupor and confusion in association with nonspecific slow wave activity on electroencephalogram have been described soon after the initiation of vigabatrin treatment. Such reactions have been fully reversible following dose reduction or discontinuation of vigabatrin (see section 4.4).

***Laboratory data indicate that vigabatrin treatment does not lead to renal toxicity. Decreases in ALT and AST, which are considered to be a result of inhibition of these aminotransferases by vigabatrin, have been observed.

Paediatric population

Psychiatric disorders

Very common: excitation, agitation

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>

In addition, you can report to Padagis via the following address: Padagis.co.il.

4.9 Overdose

Symptoms

Vigabatrin overdose has been reported. When provided, doses most commonly were between 7.5 to 30g; however, ingestions up to 90g have been reported. Nearly half of the cases involved multiple-drug ingestions. When reported the most common symptoms included drowsiness or coma. Other less frequently reported symptoms included vertigo, headache, psychosis, respiratory depression or apnea, bradycardia, hypotension, agitation, irritability, confusion, abnormal behaviour and speech disorder. None of the overdoses resulted in death.

Management

There is no specific antidote. The usual supportive measures should be employed. Measures to remove unabsorbed drug should be considered. Activated charcoal has been shown to not significantly adsorb vigabatrin in an in vitro study. . The effectiveness of hemodialysis in the treatment of vigabatrin overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03AG04

Mechanism of action

Vigabatrin is an antiepileptic drug with a clearly defined mechanism of action. Treatment with vigabatrin leads to an increase in the concentration of GABA (gamma aminobutyric acid), the major inhibitory neurotransmitter in the brain. This is because vigabatrin was designed rationally as a selective, irreversible inhibitor of GABA-transaminase, the enzyme responsible for the breakdown of GABA.

Clinical efficacy and safety

Controlled and long term clinical trials have shown that vigabatrin is an effective anticonvulsant agent when given as add on therapy in patients with epilepsy not controlled satisfactorily by conventional therapy. This efficacy is particularly marked in patients with seizures of partial origin.

Epidemiology of VFD in patients with refractory partial epilepsy was examined in an observational, open-label, multicentre, comparative, parallel group, Phase IV study, including 734 patients, at least 8 years old, with refractory partial epilepsy for at least one year.

Patients were split in three treatment groups: patients currently treated with vigabatrin (group I), patients previously exposed to vigabatrin (group II) and patients never exposed to vigabatrin (group III). The following table presents the main findings at inclusion and at the first and last conclusive evaluations in the evaluable population (n=524):

	Children (from aged 8 to 12 years old)			Adults (aged > 12 years old)		
	Group I ₁ N = 38	Group II ₂ N = 47	Group III N = 41	Group I ₃ N = 150	Group II ₄ N = 151	Group III N = 97
Visual field defect with non-identified etiology:						
-Observed at inclusion	1 (4.4%)	3 (8.8%)	2 (7.1%)	31 (34.1%)	20 (19.2%)	1 (1.4%)
-Observed at first	4 (10.5%)	6 (12.8%)	2 (4.9%)	59 (39.3%)	39 (25.8%)	4 (4.1%)

<i>conclusive evaluation</i>						
<i>-Observed at last conclusive evaluation</i>	10 (26.3%)	7 (14.9%)	3 (7.3%)	70 (46.7%)	47 (31.1%)	5 (5.2%)

¹ Median treatment duration: 44.4 months; mean daily dose: 1.48 g

² Median treatment duration: 20.6 months; mean daily dose: 1.39 g

³ Median treatment duration: 48.8 months; mean daily dose: 2.10 g

⁴ Median treatment duration: 23.0 months; mean daily dose: 2.18 g

5.2 Pharmacokinetic properties

Absorption

Vigabatrin is a water soluble compound and it is rapidly and completely absorbed from the gastrointestinal tract.

Food administration does not alter the extent of vigabatrin absorption. Time to reach maximum plasma concentrations (t_{max}) is approximately 1 hour.

Distribution

Vigabatrin is widely distributed with an apparent volume of distribution slightly greater than total body water. Binding to plasma proteins is negligible. Plasma and cerebrospinal fluid concentrations are linearly related to dose over the recommended dose range.

Biotransformation

Vigabatrin is not significantly metabolised. No metabolites have been identified in plasma.

Elimination

Vigabatrin is eliminated via renal excretion with a terminal half-life of 5-8 hours. Oral clearance (Cl/F) of vigabatrin is approximately 7 L/h (i.e. 0.10 L/h/kg). Approximately 70% of a single oral dose was recovered as unchanged drug in the urine in the first 24 hours post-dose.

Pharmacokinetic/pharmacodynamic relationships

There is no direct correlation between plasma concentration and efficacy. The duration of the effect of the drug is dependent on the GABA-transaminase re-synthesis rate.

Paediatric population

Pharmacokinetic properties of vigabatrin have been investigated in groups of six neonates (age 15-26 days), six infants (age 5-22 months) and six children (age 4.6-14.2 years) with refractory epilepsy. After administration of a single 37-50 mg/kg dose of an oral solution vigabatrin t_{max} was approximately 2.5 hours in neonates and infants, and 1 hour in children. Mean terminal half-life of vigabatrin was about 7.5 hours in neonates, 5.7 hours in infants and 5.5 hours in children. The mean Cl/F of active S-enantiomer of vigabatrin in infants and children was 0.591 L/h/kg and 0.446 L/h/kg, respectively.

5.3 Preclinical Safety Data

Animal safety studies carried out in the rat, mouse, dog and monkey have indicated that vigabatrin has no significant adverse effects on the liver, kidney, lung, heart or gastrointestinal tract.

In the brain, microvacuolation has been observed in white matter tracts of rat, mouse and dog at doses of 30 - 50 mg/kg/day. In the monkey, these lesions are minimal or equivocal. This effect is caused by a separation of the outer lamellar sheath of myelinated fibres, a change characteristic of intramyelinic oedema. In both rat and dog, the intramyelinic oedema was reversible on stopping vigabatrin treatment and even with continued treatment, histologic regression was observed. However, in rodents, minor residual changes consisting of swollen axons (eosinophilic spheroids) and mineralised microbodies have been observed. In the dog, the results of an electrophysiological study indicate that intramyelinic oedema is associated with an increase in the latency of the somatosensory evoked potential which is reversible when the drug is withdrawn.

Vigabatrin-associated retinotoxicity has only been observed in albino rats, but not in pigmented rats, dogs or monkeys. The retinal changes in albino rats were characterised as focal or multifocal disorganisation of the outer nuclear layer with displacement of nuclei into the rod and cone area. The other layers of retina were not affected. These lesions were observed in 80 to 100% of animals at the dose of 300mg/kg/day orally. The histologic appearance of these lesions was similar to that found in albino rats following excessive exposure to light. However, the retinal changes may also represent a direct drug-induced effect.

Animal experiments have shown that vigabatrin has no negative influence on fertility or pup development. No teratogenicity was seen in rats in doses up to 150mg/kg (3 times the human dose) or in rabbits in doses up to 100 mg/kg. However, in rabbits, a slight increase in the incidence of cleft palate at doses of 150 - 200 mg/kg was seen. Studies with vigabatrin revealed no evidence of mutagenic or carcinogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose, polyvinylpyrrolidone (povidone), sodium starch glycolate, magnesium stearate. Coating: Opadry® white OY-S-7298: Hydroxypropyl-methylcellulose, titanium dioxide, polyethylene glycol 8000.

6.2. 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 at cool place below 25°C. Keep in the original package.

6.5. Nature and contents of container

Clear colorless blister packs containing 10 film-coated tablets in boxes of 50, 60, or 100 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and handling

No special requirements.

7 MANUFACTURER

Padagis Israel Pharmaceuticals, Ltd., 1 Rakefet street, Shoham, Israel

8 MARKETING AUTHORISATION HOLDER

Padagis Israel Pharmaceuticals, Ltd., 1 Rakefet street, Shoham Israel

9 REGISTRATION AUTHORISATION NUMBER

058-94-27254

Revised in July 2022 according to MOH guidelines.