SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vigabatrin Zydus Pharmaceuticals UK 100 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 100 mg vigabatrin.

Excipients with known effect:

Methyl parahydroxy benzoate	1.25 mg/ml
Propyl parahydroxy benzoate	0.125 mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated.

Monotherapy in the treatment of infantile spasms (West's syndrome).

4.2 Posology and method of administration

Vigabatrin oral solution 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

Vigabatrin oral solution is for oral administration once or twice daily and may be taken before or after meals.

If the control of epilepsy is not clinically significantly improved after an adequate trial, vigabatrin treatment should not be continued. Vigabatrin should be gradually withdrawn under close medical supervision.

Adults

Maximal efficacy is usually seen in the 2-3 g/day range. A starting dose of 1 g daily should be added to the patient's current antiepileptic medicinal product regimen. The daily dose should then be titrated in 0.5 g increments at weekly intervals depending on clinical response and tolerability. The highest recommended dose is 3 g/day.

No direct correlation exists between the plasma concentration and the efficacy. The duration of the effect of the medicinal product is dependent on the rate of GABA transaminase resynthesis rather than the concentration of the drug in the plasma (see also sections 5.1 and 5.2).

Paediatric population

Resistant partial epilepsy

The recommended starting dose in neonates, children and adolescents is 40 mg/kg/day. Maintenance recommendations in relation to bodyweight are:

Bodyweight:	10 to 15 kg:	0.5-1 g/day
	15 to 30 kg:	1-1.5 g/day
	30 to 50 kg:	1.5-3 g/day
	>50 kg:	2-3 g/day

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

Monotherapy for infantile spasms (West's Syndrome)

The recommended starting dose is 50 mg/kg/day. This may be titrated over a period of one week if necessary. Doses of up to 150 mg/kg/day have been used with good tolerability.

Older people and patients with renal impairment

Since vigabatrin is eliminated via the kidney, caution should be exercised when administering the drug to the older people and more particularly in patients with creatinine clearance less than 60 ml/min. Adjustment of dose or frequency of administration should 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

Except for the treatment of infantile spasms, Vigabatrin oral solution should not be initiated as monotherapy.

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).

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 non-specific 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.

Movement disorders including dystonia, dyskinesia and hypertonia, have been reported in patients treated for infantile spasms. The benefit/risk of vigabatrin should be evaluated on an individual patient basis. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment.

As with other antiepileptic medicinal products 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 medicinal products, 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.

<u>Suicidal ideation and behaviour</u>

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 medicinal products 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.

Excipient's warning

Vigabatrin oral solution contains

methyl parahydroxybenzoate (E 218) and propyl parahydroxybenzoate (E 216) which may cause allergic reactions (possibly delayed).

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 medicinal products 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 aminoadipic 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).

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

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders		anaemia				
*Psychiatric disorders**		agitation, aggression, nervousness, depression, paranoid reaction, insomnia	hypomania, mania, psychotic disorder	suicide attempt	hallucination	
Nervous system disorders	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). Movement disorder, including dystonia, dyskinesia and

						hypertonia have been reported, either alone or in association with abnormalities in MRI (see section 4.4).
Eye disorders	visual field defect	vision blurred, diplopia, nystagmus		retinal disorder (mainly peripheral)	optic atrophy	Reduced visual acuity
Gastrointestinal disorders		nausea, vomiting, abdominal pain				
Hepato-biliary disorders					hepatitis	
Skin and subcutaneous tissue disorders		alopecia	rash	angioedema, urticaria		
Musculoskeletal and connective tissue disorders	arthralgia					
General disorders and administration site conditions	fatigue	oedema, irritability				
*Investigations****		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 non-specific 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. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Vigabatrin overdose has been reported. When provided, doses most commonly were between 7.5 to 30 g; however, ingestions up to 90 g 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 medicinal product 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 8 to 12 years old)			Adults (>12 years old)		
	Group I 1	Group II 2	Group III	Group I 3	Group II 4	Group III
	N=38	N=47	N=41	N=150	N=151	N=97
Visual field defect with non-identified aetiology:						
- Observed at inclusion	1 (4.4%)	3 (8.8%)	2 (7.1%)	31 (34.1%)	20 (19.2%)	1 (1.4%)
- Observed at first conclusive evaluation	4 (10.5%)	6 (12.8%)	2 (4.9%)	59 (39.3%)	39 (25.8%)	4 (4.1%)
- Observed at last conclusive evaluation	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 medicinal product 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 80-100% of animals at the dose of 300 mg/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 150 mg/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

Methyl para hydroxybenzoate

Propyl para hydroxybenzoate

Sucralose

Frozen peppermint (5015241T) (menthofuran, pulegone, estragole)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

After the first opening of the bottle: 90 days.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Vigabatrin 100 mg/ml oral solution is packaged in white opaque HDPE bottle with polypropylene 28 mm white child resistant closures with an induction seal liner containing 150 ml of the liquid.

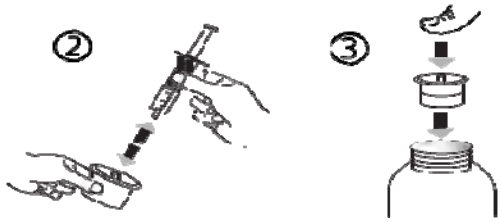
The package also contains a 10 ml oral syringe printed with markings at every 1.0 ml and graduated at every 0.25 ml together with an adaptor.

6.6 Special precautions for disposal

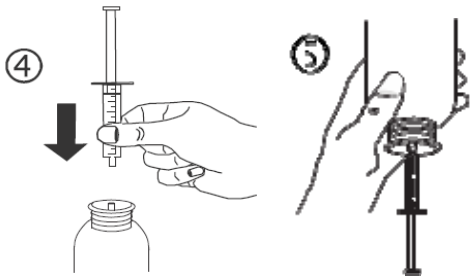
Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use

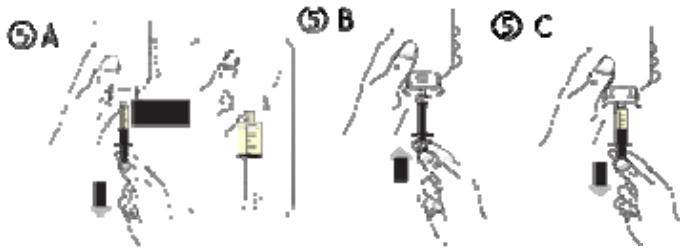
- Open the bottle: press the cap and turn it anti clockwise (figure 1)



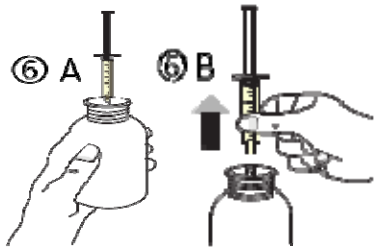
- Separate the adaptor from the syringe (figure 2). Insert the adaptor into the bottle neck (figure 3). Ensure it is well fixed.



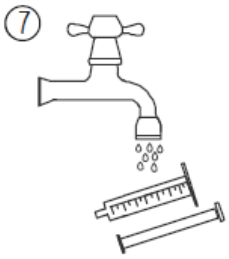
- Take the syringe and put it in the adaptor opening (figure 4). Turn the bottle upside down (figure 5).



- Fill the syringe with a small amount of oral solution by pulling the piston down (figure 5A), then push the piston upward in order to remove any possible bubble (figure 5B). Pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor (figure 5C).



- Turn the bottle the right way up (figure 6A). Remove the syringe from the adaptor (figure 6B).



- Close the bottle with the plastic screw cap.
- To take a dose the quantity of solution is dissolved in half a drinking glass full of cold water or soft drink, like juice or milk.
- After dosing, wash the syringe with water only (figure 7).

7 MARKETING AUTHORISATION HOLDER

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Northampton

NN7 4PP, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 58839/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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