# Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

# (Vigabatrin)

# Sabril, Sabrilex

# FI/W/003/pdWS/001

| | |
|---|---|
| **Rapporteur:** | Finland (FI) |
| **Finalisation procedure (day 120):** | 19.12.2013 |
| **Date of finalisation of PAR** | 21.02.2014 |

# TABLE OF CONTENTS

**ADMINISTRATIVE INFORMATION**

| | |
|---|---|
| Invented name of the medicinal products: | See section VI |
| INN (or common name) of the active substance: | Vigabatrin |
| MAHs: | See section VI |
| Pharmaco-therapeutic group (ATC Code): | Antiepileptics (N03AG04) |
| Pharmaceutical forms and strengths: | Film-coated tablets, 500 mg;<br>Granules for oral solution, 500 mg |

# I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2, 4.6, 4.8 and 5.2 and PL changes in sections 2, 3 and 4.

**Summary of outcome**

☐ No change

☒ Change

☐ New study data

☐ New safety information

☒ Paediatric information clarified: SmPC sections 4.2, 4.6, 4.8 and 5.2; PL sections 2, 3 and 4

☐ New indication

# II. RECOMMENDATION[1]

SmPC changes are proposed in sections 4.2, 4.6, 4.8 and 5.2 and PL changes in sections 2, 3 and 4 in order to clarify recommendations on paediatric use of vigabatrin.

Type IB variation is requested from the MAHs involved in the worksharing within 60 days after finalisation of the procedure to implement the proposal and amend the marketing authorisation as necessary.

Recommended major changes in the **SmPC** are presented below:

## 4.2 Posology and method of administration

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.

## 4.6 Fertility, pregnancy and lactation

*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.

[1] *The recommendation from section V can be copied in this section*.

*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).

<TRADENAME> 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 <TRADENAME> 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).

## 4.8 Undesirable effects

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 | | | | |
| ... | | | | | | |
| *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 the national reporting system listed in Appendix V.

## 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.

Recommended minor changes in the **SmPC** and **PL**:

Additional changes, such as updates according to the SmPC guideline and the latest QRD template including appendices and corresponding changes in the PL are proposed.

# III. INTRODUCTION

Vigabatrin
Vigabatrin is an antiepileptic drug (AED). Treatment with vigabatrin leads to an increase in the concentration of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. This is because vigabatrin is an irreversible inhibitor of GABA-transaminase, the enzyme primarily responsible for the catabolism of GABA. The duration of the anticonvulsant effect of vigabatrin is presumed to be dependent on regeneration of GABA-transaminase activity.

Current therapeutic indications of vigabatrin are:

- Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalisation, that is where all other appropriate drug combinations have proved inadequate or have not been tolerated.
- Monotherapy in the treatment of infantile spasms (West's syndrome).

Treatment of infantile spasms is an exclusively paediatric indication.

In children, the recommended starting dose is 40 mg/kg/day in combination therapy for partial epilepsy and 50 mg/kg/day in monotherapy for infantile spasms. Maintenance doses of up to 150 mg/kg/day have been used to treat infantile spasms.

Regulatory history
Vigabatrin was originally approved for use as add-on treatment for drug-resistant epilepsies in 1989. In 1997, three cases of severe visual field defects (VFDs) were reported in patients

treated with vigabatrin. A subsequent follow-up study reported a prevalence of visual field constriction in thirteen of thirty-two patients (40 %).

In 1998, a referral concerning the risk-benefit assessment of vigabatrin was arranged. In 1999, the former Committee for Human Medicinal Products (CHMP) recommended a number of changes to the product labelling. The indications mentioned above were retained in the 15 EU States included in the "Mutual Recognition Procedure." The CHMP also mandated the MAH to perform a number of preclinical and clinical studies in order to estimate with greater precision the risk of VFDs in patients treated with vigabatrin. Commitments undertaken with respect to the Article 12 procedure are now considered to have been concluded.

Article 45 paediatric assessment of vigabatrin
The MAH submitted 19 non-clinical and 86 clinical documents including study reports, literature references and other documents related to paediatric studies for vigabatrin, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for vigabatrin and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the clinical studies

Vigabatrin tablet and granules for oral solution formulations in strength of 500 mg.

For paediatric use, sachet contents (*i.e.*, the granules for oral solution) may be placed in different beverages (*e.g.*, water, fruit juice or milk).

## IV.2 Non-clinical aspects

### 1. Introduction

The MAH submitted reports for:

- The Initial MAA - Sabril Tablets (500 mg), Part III, Volume 1, Summary, Toxicological and Pharmacological Documentation, 1988;
- The MAA - Sabril Tablets (500 mg), Part 1C2, Expert Report, Toxicological and Pharmacological Documentation, 1987;

- A 2 Week Oral Range Finding Toxicity Study In Juvenile Rats;
- A 4 Week Oral Ocular Toxicity Study In Juvenile Rats (From Postnatal Day 4);
- A 2 Week Oral Exploratory Toxicity Study In Rats;
- A 13 Week Oral Ocular Toxicity Study In Sprague Dawley Rats With An Interim Necropsy At 4 Weeks And A 4 Week Recovery Period;

- An Annual Update on Preclinical activities - Sabril/Sabrilex®. Vigabatrin Article 12 Referral Procedure Commitments, 2004;

- Bittigau P et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U S A 2002; 99: 15089-94;
- Bittigau P et al. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci 2003; 993: 103-14;
- Jammoul F et al. Taurine deficiency damages photoreceptors and retinal ganglion cells in vigabatrin-treated neonatal rats. Mol Cell Neurosci 2010; 43: 414-21;
- Levav T et al. Perinatal exposure to GABA-transaminase inhibitor impaired psychomotor function in the developing and adult mouse. Int J Dev Neurosci 2004; 22: 137-47;
- Levav T et al. Impaired synaptogenesis and longterm modulation of behavior following postnatal elevation of GABA levels in mice. Neuropharmacology 2008; 54: 387-98;
- Levav-Rabkin T et al. A Sensitive Period of Mice Inhibitory System to Neonatal GABA Enhancement by Vigabatrin is Brain Region Dependent. Neuropsychopharmacology 2010; 35: 1138-54;
- Melamed O et al. Glutamatergic synaptogenesis following neonatal potentiation of GABA in mice. J Mol Neurosci 2009; 39(Suppl 1): S79;
- Qiao M et al. Effect of longterm vigabatrin administration on the immature rat brain. Epilepsia 2000; 41: 655-65;
- Sidhu RS et al. Low-Dose Vigabatrin (gamma-vinyl GABA)-Induced Damage in the Immature Rat Brain. Exp Neurol 1997; 144(2): 400-5;

- Walzer M et al. Oral toxicity of vigabatrin in immature rats: Characterization of intramyelinic edema. Neurotoxicology 2011; 32: 963-74

- FDA CDER Medical Review 20-427, 2009;
- FDA CDER Summary Review 22-006, 2009

**2. Non-clinical studies**

Non-published, internal studies:

**The Initial MAA - Sabril Tablets (500 mg), Part III, Volume 1, Summary, Toxicological and Pharmacological Documentation, 1988;**
**The MAA - Sabril Tablets (500 mg), Part 1C2, Expert Report, Toxicological and Pharmacological Documentation, 1987**
**A 2 Week Oral Range Finding Toxicity Study In Juvenile Rats**
**A 4 Week Oral Ocular Toxicity Study In Juvenile Rats (From Postnatal Day 4);**
**A 2 Week Oral Exploratory Toxicity Study In Rats;**
**A 13 Week Oral Ocular Toxicity Study In Sprague Dawley Rats With An Interim Necropsy At 4 Weeks And A 4 Week Recovery Period;**
**An Annual Update on Preclinical activities - Sabril/Sabrilex®. Vigabatrin Article 12 Referral Procedure Commitments, 2004**

These relatively old peri- and post-natal studies and ocular toxicity studies in juvenile rats did not provide new non-clinical information necessitating changes in the product information.

Published studies

**Bittigau P et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U S A 2002; 99: 15089-94**

**Results**: This study revealed that phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, and valproate cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans. Neuronal death was associated with reduced expression of neurotrophins and decreased concentrations of survival-promoting proteins in the brain.

**Bittigau P et al. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci 2003; 993: 103-14**
**Description and Methods**: This study investigated whether common AEDs cause neurodegeneration in the developing rat brain. Rats aged 3-30 days received phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, or valproic acid.
**Results**: Histologic examination of the brains revealed that these drugs cause widespread and dose-dependent apoptotic neurodegeneration in the developing rat brain. Apoptotic neurodegeneration was triggered at plasma drug levels relevant for seizure control in humans. AEDs lead to reduced expression of neurotrophins and decreased concentrations of the active forms of ERK1/2, RAF, and AKT. beta-Estradiol, which stimulates pathways that are activated by neurotrophins, ameliorated AEDs-induced neurodegeneration. The findings present one possible mechanism to explain cognitive impairment and reduced brain mass associated with pre- or postnatal exposure of humans to antiepileptic therapy.

**Jammoul F et al. Taurine deficiency damages photoreceptors and retinal ganglion cells in vigabatrin-treated neonatal rats. Mol Cell Neurosci 2010; 43: 414-21**
**Description and Methods**: The anti-epileptic drug vigabatrin induces an irreversible constriction of the visual field, but is still widely used to treat infantile spasms and some forms of epilepsy. A study recently reported that vigabatrin-induced cone damage is due to a taurine deficiency. However, optic atrophy and thus retinal ganglion cell degeneration was also reported in children treated for infantile spasms.
**Results**: This study showed in neonatal rats treated from postnatal days 4 to 29 that the vigabatrin treatment triggers not only cone photoreceptor damage, disorganisation of the photoreceptor layer and gliosis but also retinal ganglion cell loss. In the neonatal rats, taurine supplementation partially prevents retinal lesions and the retinal ganglion cell loss. The results provided evidence of possible retinal ganglion cell neuroprotection by taurine. The authors suggest that taurine should be administered with vigabatrin for infantile spasms or epilepsy.

**Levav T et al. Perinatal exposure to GABA-transaminase inhibitor impaired psychomotor function in the developing and adult mouse. Int J Dev Neurosci 2004; 22: 137-47**
**Description and Methods**: This study examined the vulnerability of the developing brain to treatment with one of the new antiepileptic drugs--vigabatrin--during two time periods in newborn mice (postnatal days 1-7 and 4-14) which parallel the third trimester of human embryo brain development.
**Results**: Delayed development of sensory and motor reflexes, reduced mobility, impaired object recognition and deficient spatial learning and memory were observed. Specific susceptibility to the age of exposure was detected in various motor functions. A number of morphological correlates may explain these behavioral alterations; a transient increase in CA1 pyramidal cell layer and decrease in granular cell layer in hippocampus were detected at postnatal day 7. In addition, a significantly lower cell density was observed in the adult mouse brain in all layers of the M2 cerebral cortex of mice treated during days 4-14, compared to the controls. The findings demonstrated short- and long-term deleterious effects of vigabatrin treatment and suggest a specific vulnerability during the first postnatal week.

**Levav T et al. Impaired synaptogenesis and longterm modulation of behavior following postnatal elevation of GABA levels in mice. Neuropharmacology 2008; 54: 387-98**

**Description and Methods**: This study investigated the time course in which postnatal vigabatrin (GVG) treatment induced behavioral changes in an open field test and had a detrimental developmental effect on recognition memory in mice.
**Results**: GVG treatment significantly modulated the expression of synaptobrevin/vesicle-associated membrane protein (VAMP) II and synaptotagmin (Synt) I. A short-term decrease in the expression of these proteins was followed by a long-term elevation in their expression in both the hippocampus and the cerebral cortex. The changes observed in synaptogenesis may explain the behavioral impairment induced by postnatal GVG treatment and suggest a possible mechanism for the detrimental effect of AEDs acting through elevation of GABA levels.

**Levav-Rabkin T et al. A Sensitive Period of Mice Inhibitory System to Neonatal GABA Enhancement by Vigabatrin is Brain Region Dependent. Neuropsychopharmacology 2010; 35: 1138-54**
**Description and Methods**: This study examined immediate and long-lasting influences of exposure to the GABA-potentiating drug vigabatrin (GVG) on the GABAergic system in the hippocampus and cerebral cortex, before and during the developmental switch in GABA function (postnatal days P1-7 and P4-14).
**Results**: GVG induced a transient elevation of GABA levels. Cumulatively, the results suggested a particular susceptibility of the hippocampus to GVG when exposed during days P4-14. The studies identified modifications of key components in the inhibitory system during a critical developmental period. The findings provided novel insights into the deleterious consequences observed in children following prenatal and neonatal exposure to GABA-potentiating drug

**Melamed O et al. Glutamatergic synaptogenesis following neonatal potentiation of GABA in mice. J Mol Neurosci 2009; 39 (Suppl 1): S79**
**Description and Methods:** A developmental switch in the function of GABA from depolarizing to hyperpolarizing occurs in the immature brain. The excitatory nature of GABA during this period plays a crucial role in wiring of neuronal circuits. This study hypothesized that neonatal GABA enhancement during postnatal days (P) 1-7 or P4-14, before or during the switch in GABA function, may modify activity dependent synaptogenesis. To elevate GABA levels Vigabatrin (GVG, 50 mg/kg) was injected daily to newborn balb/c mice (sc.)
**Results:** The authors of this abstract concluded that AMPA and monoamine neurotransmission susceptibility to neonatal GABA potentiation may underlie long-lasting behavioral impairment previously reported following early exposure to GVG.

**Qiao M et al. Effect of longterm vigabatrin administration on the immature rat brain. Epilepsia 2000; 41: 655-65**

**Description and Methods**: This study aimed to determine whether the neuropathologic changes produced by vigabatrin (VGB) administration in the developing rat brain are reversible. Rats were injected daily with VGB (25-40 mg/kg/day, s.c.) from age 12 days for 2 weeks followed by 2 weeks of a drug-free period.
**Results**: At the end of 2 weeks' VGB administration: (a) there was a hyperactivity and a shortened latency to escape out of cool water; (b) white matter appeared hyperintense in T2 and diffusion-weighted MR images; (c) microvacuolation, TUNEL-positive nuclei, and swollen axons were observed in the corpus callosum; (d) myelin staining indicated a reduction in myelination, as did the reduction in activities of myelin and oligodendrocyte-associated enzymes and the decrease in myelin basic protein. Two weeks after stopping VGB administration: (a) MR images were normal, and microvacuolation was no longer in the white matter; (b) reduction in myelination reversed partially; (c) the T2 relaxation time remained elevated in the hypothalamus; and (d) the behavioral response remained abnormal. Long-term VGB administration to young rats seems to cause brain injury, which recovers partially on its cessation. The observed cell

death, disrupted myelination, and alterations in behavior indicate a need for further safety assessment in infants and children.

**Sidhu RS et al. Low-Dose Vigabatrin (gamma-vinyl GABA)-Induced Damage in the Immature Rat Brain. Exp Neurol 1997; 144(2): 400-5**
**Description and Methods**: This study hypothesized that vigabatrin might adversely affect myelination in the developing brain. Rats were given vigabatrin in doses comparable to those used clinically (15-50 mg/kg/day), from age 12 to 16 days, and killed at age 19-20 days.
**Results:** The study observed decreased myelin staining in the external capsule, axonal degeneration in white matter, evidence of glial cell death in the white matter, and reactive astrogliosis in the frontal cortex. The findings indicate that vigabatrin can have adverse and potentially irreversible effects on the developing rat brain. The mechanism of damage could be direct toxicity of vigabatrin or an indirect effect mediated through elevated GABA levels.

**Walzer M et al. Oral toxicity of vigabatrin in immature rats: Characterization of intramyelinic edema. Neurotoxicology 2011; 32: 963-74**
**Description:** Two toxicologic studies of vigabatrin were conducted with immature Sprague Dawley rats to characterize intramyelinic edema (IME) formation. Study 1 was a dosage-ranging characterization of overall toxicity of vigabatrin in young, developing rats. Study 2 evaluated vacuolar brain lesions found in Study 1.
**Methods:** During Study 1, immature Sprague Dawley rats were orally administered deionized water, or vigabatrin at 5, 15, or 50mg/kg/day for ≤ 9 weeks, beginning at postnatal day 4 (PND 4). Toxicologic observations were collected, including adverse clinical signs, body weight gains, food consumption, ophthalmoloscopy, electroretinograms, sexual maturation, motor activity, memory, and learning behaviors. CNS tissues were examined by light microscopy for evidence of IME. In Study 2, immature rats were again administered vigabatrin (50mg/kg/day for ≤ 9 weeks, beginning at PND 4). CNS tissues were examined by microscopy for evidence of IME.
**Results:** At 5-50mg/kg/day, dosage-related reduced food consumption, decreased body weight, and delayed sexual maturation were found. Effects were more pronounced in males. Increased degrees of vacuolation were observed on PND 67 only after a dosage of 50mg/kg/day, and were attenuated during recovery. Vacuolar-change morphology was characteristic of IME, with no evidence of cellular or neuritic degeneration. Hypomyelination and gliopathy were noted from PNDs 4-15, and were likely related to vigabatrin exposure during active myelination. Vacuolation was markedly attenuated in post-recovery-period rats.
**Conclusions**: The studies indicated toxicities in young rats at vigabatrin dosages lower than those reported for toxicities in older rats. Dosages <50mg/kg/day did not affect CNS, behavior, and reproductive development. At the greatest dosage, some retardation of physical growth, delay in sexual maturation, reduction in physical strength, and induction of CNS stimulation (handling-induced spasms) occurred. The key pathologic finding was vacuolar brain lesions in the white and gray matter, which generally reversed upon drug discontinuation. Vacuoles were confined to myelin sheaths. Vigabatrin delayed myelination, an effect greatest during active myelination.

Other documents:

**FDA CDER Medical Review 20-427, 2009;**
**FDA CDER Summary review 22-006, 2009**
These two reviews submitted by the MAH as part of the Art 45 submission present an FDA neuropathologist opinion regarding the lesions observed in the brain of juvenile rats in the study by Walzer et al., 2011, summarized above.

### 3. Discussion on non-clinical aspects and conclusion

Regarding non-clinical studies, the MAH concluded that young rats appear to have a greater sensitivity than adults to systemic, retinal and neuronal effects of vigabatrin. In neonatal/juvenile rats, lesions were also identified in a number of brain gray matter locations in addition to white matter lesions seen in adult rats.

It remains unclear whether the lesions seen in the juvenile rat in the deep gray matter (in the same anatomic locations as the MRI lesions in paediatric patients) represent neuronal degeneration. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg/day) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in paediatric patients receiving an oral dose of 50 mg/kg. The clinical relevance of animal findings is still uncertain and should be put in perspective with the information available from children treated with vigabatrin that represents the most relevant information to assess the safety of vigabatrin in paediatric patients.

Findings of non-clinical studies relevant for use in the paediatric population have been included in relevant sections of the present SmPC in a manner comprehensive enough. The clinical relevance of some of the most recent studies, such as the study by Walzer et al., 2011, remains unclear. Therefore, at the present time, addition of these findings to the SmPC does not add to the information needed by the prescriber or the children / their caregivers.

## IV.3 Clinical aspects

### 1. Introduction

The MAH submitted reports for:


- Chiron C, Dulac O. Drug therapy for West's syndrome. Adv Exp Med Biol 2002; 497: 51-6;
- Dulac O, Tuxhorn I. Infantile spasms and West syndrome. In Epileptic syndromes in infancy, childhood and adolescence (3rd Edition). Roger J et al. (eds). John Libbey & C° Ltd, Eastleigh, UK 2002; pp 47-63;
- Mackay M et al. Treatment of infantile spasms: an evidence-based approach. Int Rev Neurobiol 2002; 49: 157-84;
- Overby PJ, Kossoff EH. Treatment of infantile spasms. Curr Treat Options Neurol 2006; 8: 457-64;
- Curatolo P et al. Management of epilepsy in tuberous sclerosis complex. Expert Rev Neurother 2008; 8: 457-67;
- Horvath KM et al. Treatment of the West syndrome. Tijdschr Kindergeneeskd 2007; 75: 220-5;
- Parisi P et al. Current role of vigabatrin in infantile spasms. Eur J Paediatr Neurol 2007; 11: 331-6;
- Wheless JW et al. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord 2007; 9: 353-412;
- Hancock EC et al. Treatment of infantile spasms. Cochrane Database Syst Rev 2008: CD001770;
- Tsao CY. Current trends in the treatment of infantile spasms. Neuropsychiatr Dis Treat 2009; 5: 289-99;
- Tolman JA, Faulkner MA. Vigabatrin: a comprehensive review of drug properties including clinical updates following recent FDA approval. Expert Opin Pharmacother 2009; 10: 3077-89;

- Moran NF et al. Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. Seizure 2004; 13: 425-33;
- Darke K et al.; Trial steering committee on behalf of participating investigators. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomized trial. Arch Dis Child 2010; 95: 382-6;
- Glauser T et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006; 47: 1094-120;
- Mackay MT et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004; 62: 1668-81;
- Pellock JM et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010; 51: 2175-89;

- Rey E et al. Pharmacokinetics of the individual enantiomers of vigabatrin (gamma-vinyl GABA) in epileptic children. British Journal of Clinical Pharmacology 1990, 30: 253-257;

- Chiron C et al. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res 1997; 26: 389-95;
- Vigevano et Cilio. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia 1997; 38: 1270-4;
- Appleton RE et al. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia 1999; 40: 1627-33;
- Elterman RD, Shields WD, Mansfield KA, Nakagawa J; US Infantile Spasms Vigabatrin Study Group. Randomized trial of vigabatrin in patients with infantile spasms. Neurology 2001; 57: 1416-21;
- Elterman RD et al. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial.J Child Neurol 2010; 25: 1340-7;
- Askalan R et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. J Child Neurol 2003; 18: 165-70;
- Lux AL et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 2004; 364: 1773–8;
- Lux AL et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol 2005; 4: 712–17;
- Chiron C et al. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991; 6(Suppl 2): S52-9;
- Aicardi J et al. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. Sabril IS Investigator and Peer Review Groups. Epilepsia 1996; 37: 638-42;
- Granström ML et al. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. Epilepsia 1999; 40: 950-7;
- Antoniuk SA et al. [West syndrome: clinical and electroencephalographic follow up of 70 patients and response to its treatment with adrenocorticotropic hormone, prednisone, vigabatrin, nitrazepam and valproate]. Arq Neuropsiquiatr 2000; 58: 683-90;
- Ibrahim S et al. Clinical profile and treatment of infantile spasms using vigabatrin and ACTH--a developing country perspective. BMC Pediatr 2010; 10:1;

- Chiron C et al. Vigabatrin withdrawal randomized study in children. Epilepsy Res 1996; 25: 209-15;
- Zamponi et al. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. Arch Neurol 1999; 56: 605-7;

- Sobaniec et al. A comparative study of vigabatrin vs. carbamazepine in monotherapy of newly diagnosed partial seizures in children. Pharmacol Rep 2005; 57: 646-53;
- Luna D et al. Vigabatrin in the treatment of childhood epilepsies: a single-blind placebo-controlled study. Epilepsia 1989; 30: 430-7;
- Dulac O et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; 6(Suppl 2): S30-7;
- Herranz JL et al. Dose-response study of vigabatrin in children with refractory epilepsy. J Child Neurol 1991; Suppl 2: S45-51;
- Dalla Bernardina B et al. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. Epilepsia 1995; 36: 687-91;
- Gram L et al. Gamma-Vinyl GABA: a double-blind placebo-controlled trial in partial epilepsy. Ann Neurol 1985; 17: 262-6;
- Loiseau P et al. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia 1986; 27: 115-20;
- Tassinari CA et al. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987; 44: 907-10;
- Grünewald RA et al. Effects of vigabatrin on partial seizures and cognitive function. J Neurol Neurosurg Psychiatry 1994; 57: 1057-63;
- Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. Lancet 1999; 354: 13-9;
- Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. Epilepsy Res 1999; 34: 199-205;
- Lindberger M et al. Gabapentin versus vigabatrin as first add-on for patients with partial seizures that failed to respond to monotherapy: a randomized, double-blind, dose titration study. GREAT Study. Epilepsia 2000; 41(10): 1289-95;
- Sivenius MR et al. Double-blind dose reduction study of vigabatrin in complex partial epilepsy. Epilepsia 1987; 28: 688-92;
- Uldall P et al. Vigabatrin in pediatric epilepsy--an open study. J Child Neurol 1991; Suppl 2: S38-44;
- Gibbs JM et al. Vigabatrin in intractable childhood epilepsy: a retrospective study. Pediatr Neurol 1992; 8: 338-40;
- Gherpelli JL et al. Vigabatrin in refractory childhood epilepsy. The Brazilian Multicenter Study. Epilepsy Res 1997; 29: 1-6;
- Coppola G et al. Vigabatrin as add-on therapy in children and adolescents with refractory epilepsy: an open trial. Brain Dev 1997; 19: 459-63;
- Nabbout RC et al. Vigabatrin in partial seizures in children. J Child Neurol 1997; 12: 172-7;

- Cramer JA et al. New antiepileptic drugs: comparison of key clinical trials. Epilepsia 1999; 40: 590-600;
- Devinsky O, Cramer J. Safety and efficacy of standard and new antiepileptic drugs. Neurology 2000; 55(Suppl 3): S5-10;
- Sander JW. The use of antiepileptic drugs--principles and practice. Epilepsia 2004; 45 Suppl 6: 28-34;
- Remy C, Beaumont D. Efficacy and safety of vigabatrin in the long-term treatment of refractory epilepsy. Br J Clin Pharmacol 1989; 27 Suppl 1: 125S-129S;

- An open multicentre study of the prevalence, incidence and clinical course of visual field defects in adults and children with refractory partial epilepsy treated with antiepileptic drugs. Clinical Study Report, 16-Jun-2009;
- Kankirawatana P et al. Vigabatrin therapy in infantile spasms. J Med Assoc Thai 2002; 85(Suppl 2): S778-83;

- Moraes MHP et al. Efficacy and tolerability of vigabatrin in West syndrome. Arquivos de Neuro-Psiquiatria 2005; 63(2B): 469-73;
- Turanli G et al. Vigabatrin in paediatric patients with refractory epilepsy. Turk J Pediatr 2006; 48(1): 25-30;
- Aurich-Barrera B et al. Paediatric Prescrition-Event Monitoring (PEM) and its role in risk management: Results of a modified PEM study on lamotrigine and vigabatrin. Drug safety 2006; 29: 911-1010 (Abs 112);
- Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. J Child Neurol 2007; 22: 1360-6;
- Camposano SE et al. Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile. Epilepsia 2008; 49: 1186-91;
- Cohen-Sadan S et al. Multicenter long-term follow-up of children with idiopathic West syndrome: ACTH versus vigabatrin. Eur J Neurol 2009; 16: 482-7;
- Kwon YS et al. Combined treatment with topiramate and vigabatrin in idiopathic infantile spasms. Eur J Neurol 2009;16(S3): AbsP2430;
- Harding GFA et al. Vigabatrin; Its effect on the electrophysiology of vision. Documenta Ophthalmologica 2002; 104: 213-29;
- Harding GFA et al. Field-specific visual-evoked potentials: Identifying field defects in vigabatrin-treated children. Neurology 2002; 58: 1261-5;
- Vanhatalo S et al. Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia 2002; 43: 748-56;
- Westall CA et al. The Hospital for Sick Children, Toronto, longitudinal ERG study of children on vigabatrin. Documenta Ophthalmologica 2002; 104: 133-49;
- Hammoudi DS et al. Reduced visual function associated with infantile spasms in children on vigabatrin therapy. Invest Ophthalmol Vis Sci 2005; 46: 514-20;
- Werth R, Schadler G. Visual field loss in young children and mentally handicapped adolescents receiving vigabatrin. Invest Ophthalmol Vi Sci. 2006; 47: 3028-35;
- You S.J. Vigabatrin and visual field defects in children with epilepsy. J Korean Med Sci 2006; 21: 728-32;
- Gaily E et al. Visual fields in children treated with vigabatrin in infancy. Epilepsia 2006; 47(Suppl.4): 179-80(Abs.2176);
- Mirabella G et al. Contrast sensitivity is reduced in children with infantile spasms. Invest Ophthalmol Vis Sci. 2007; 48: 3610-5;
- Durbin S et al. Reduced grating acuity associated with retinal toxicity in children with infantile spasms on vigabatrin therapy. Invest Ophthalmol Vis Sci 2009; 50: 4011-6;
- Wohlrab G et al. Vigabatrin therapy in infantile spasms: solving one problem and inducing another? Epilepsia 2009; 50(8): 2006-8;
- Chiron C, Dulac O et al. Magnetic resonance imaging in epileptic children treated with vigabatrin. Epilepsia 1989; 30: 736;
- Pearl PL et al. MRI Abnormalities Associated with Vigabatrin Therapy: Higher Risk in Infants? Epilepsia 2006; 47(S4): 14(Abs. PH.04);
- Desguerre I et al. Transient magnetic resonance diffusion abnormalities in West syndrome: the radiological expression of non-convulsive status epilepticus? Dev Med Child Neurol 2008; 50: 112-6;
- Dracopoulos A et al. The reversible neurotoxicity of vigabatrin in infantile spasms. Epilepsia 2008; 49(Suppl 7): 86;
- Wheless JW et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. Epilepsia 2009; 50: 195-205;
- Dracopoulos A et al. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. Epilepsi. 2010;51(7):1297-304;
- Vallat C et al. Treatment with vigabatrin may mimic a-aminoadipic aciduria. Epilepsia 1996; 37(8): 803-5;

- Kuenzle Ch et al. Adverse effects of vigabatrin in Angelman syndrome. Epilepsia 1998; 39: 1213-5;
- Zelnik N et al. Vigabatrin, lamotrigine, topiramate and serum carnitine levels. Pediatr Neurol 2008; 39: 18-21;

- Yagi K. Overview of Japanese experience-controlled and uncontrolled trials. Seizure 2004; 13 Suppl 1: S11-5;
- Yamauchi T, Aikawa H. Efficacy of zonisamide: our experience. Seizure 2004; 13 Suppl 1: S41-8; discussion S49;

The MAH submitted an extended synopsis for:

- A follow-up screening to investigate the occurence of long-term retinal effect in children exposed to vigabatrin treatment and in subjects exposed to vigabatrin in utero. Clinical Study Report, Sept-2000

## 2. Clinical studies

Therapeutic positioning

*West syndrome*

**Chiron C, Dulac O. Drug therapy for West's syndrome. Adv Exp Med Biol 2002; 497: 51-6;**
**Dulac O, Tuxhorn I. Infantile spasms and West syndrome. In Epileptic syndromes in infancy, childhood and adolescence (3rd Edition). Roger J et al. (eds). John Libbey & C° Ltd, Eastleigh, UK 2002; pp 47-63;**
**Mackay M et al. Treatment of infantile spasms: an evidence-based approach. Int Rev Neurobiol 2002; 49: 157-84;**
**Overby PJ, Kossoff EH. Treatment of infantile spasms. Curr Treat Options Neurol 2006; 8: 457-64;**
**Curatolo P et al. Management of epilepsy in tuberous sclerosis complex. Expert Rev Neurother 2008; 8: 457-67;**
**Horvath KM et al. Treatment of the West syndrome. Tijdschr Kindergeneeskd 2007; 75: 220-5;**
**Parisi P et al. Current role of vigabatrin in infantile spasms. Eur J Paediatr Neurol 2007; 11: 331-6;**
**Wheless JW et al. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord 2007; 9: 353-412;**
**Hancock EC et al. Treatment of infantile spasms. Cochrane Database Syst Rev 2008: CD001770;**
**Tsao CY. Current trends in the treatment of infantile spasms. Neuropsychiatr Dis Treat 2009; 5: 289-99;**
**Tolman JA, Faulkner MA. Vigabatrin: a comprehensive review of drug properties including clinical updates following recent FDA approval. Expert Opin Pharmacother 2009; 10: 3077-89;**

*Partial epilepsy*

**Moran NF et al. Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. Seizure 2004; 13: 425-33;**
**Darke K et al.; Trial steering committee on behalf of participating investigators. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomized trial. Arch Dis Child 2010; 95: 382-6;**

*Practice guidelines*

**Glauser T et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006; 47: 1094-120;**

**Mackay MT et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004; 62: 1668-81;**

**Pellock JM et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010; 51: 2175-89**

The MAH submitted 16 studies listed above regarding the therapeutic positioning of vigabatrin. The documents are mostly journal articles and reviews or book chapters published in years 2002–2010.

Based on the above references the MAH concluded that concerning monotherapy in West syndrome, vigabatrin is considered to provide rapid and effective seizure control. Corticosteroids and adrenocorticotropic hormone (ACTH) are also useful in the management of West syndrome. Recent opinion concurs that vigabatrin is the preferred treatment in infantile spasms due to tuberous sclerosis.

Concerning partial epilepsy with or without secondary generalization the MAH concluded that the therapeutic positioning of vigabatrin is in the treatment of patients with resistant partial epilepsy in combination with other anti-epileptic drugs when all other appropriate drug combinations have proved inadequate or have not been tolerated. Although demonstrated to be effective, the side-effect profile of vigabatrin is unfavourable compared to other treatment options.

Concerning official recommendations, the International League against Epilepsy (ILAE) has noted that there is "an alarming lack of well-designed, properly conducted randomised clinical trials, especially for generalized seizures/epilepsies and in children" and it is therefore difficult to develop evidence-based guidelines aimed at identifying optimal AED treatment strategies. The American Academy of Neurology (AAN) concluded in 2004 that ACTH was probably an effective agent in the short-term treatment of infantile spasms and vigabatrin was possibly effective. With regard to long-term treatment, it was considered that data were insufficient to make any recommendation.

In conclusion, vigabatrin has been used to treat infantile spasms effectively, particularly those associated with tuberous sclerosis. In partial epilepsy, adverse effects limit the usefulness of vigabatrin as first- or even second-line agent.

Clinical pharmacology

**Rey E et al. Pharmacokinetics of the individual enantiomers of vigabatrin (gamma-vinyl GABA) in epileptic children. British Journal of Clinical Pharmacology 1990, 30: 253-257;**

Pharmacokinetic profile of vigabatrin in adults is well established. There is one study by Rey et al., 1990, that aimed to document possible age-related differences in vigabatrin pharmacokinetics in epileptic children and to determine the enantio-specificity in this population. The authors concluded that "…the absence of significant differences in the kinetic parameters of vigabatrin…between the two groups [Group 1: 5–22 months; Group 2: 4.6–14.2 years] does not support the use of a different dosage regimen according to age between 1 month and 15 years of age."

Concerning pharmacokinetic parameters, the MAH reports that after administration of a single dose of vigabatrin in infants, tmax is approximately 2.5 hours while tmax in children is similar to the one documented in adults (approximately 1 hour). t1/2 of vigabatrin is about 5.7 hours in infants as compared to 7.5 hours in adults. The clearance in infants and children is 2.4 ± 0.8 and 5.7 ± 2.5 L/h, respectively compared to 7 L/h in adults.

Following the present Art. 45 evaluation, pharmacokinetic studies in different paediatric age groups should be summarized, with a comparison to adults and taking also into account the study by Vauzelle-Kervroedan et al. (Pharmacokinetics of the individual enantiomers of vigabatrin in neonates with uncontrolled seizures. Br J Clin Pharmacol 1996; 42: 779-781). Wording of the SmPC section 5.2 should be amended accordingly.

Efficacy

*Studies in West syndrome*

Six randomised clinical trials have evaluated the efficacy of vigabatrin in the treatment of infantile spasms (Table 1). These included a total of 367 children. Vigabatrin was compared to placebo, to hydrocortisone and to either ACTH or methylprednisolone in one trial each and to ACTH alone in two trials. The remaining study compared two doses of vigabatrin. Only the placebo-controlled trial was performed under a double-blind. Five non-randomised studies are also included in Table 1 as ”Other supportive studies”. Main methods of the studies are presented in Table. Results of each study are briefly summarized in the text below.

**Table 1**. Clinical studies of vigabatrin in the treatment of infantile spasms (West Syndrome)

| Study | N | Age range | Design | Comparator | Daily dose of VGB | Primary end-point |
|---|---|---|---|---|---|---|
| *Randomised clinical trials* | | | | | | |
| Chiron 1997 (42) | 22 | 1 mo - 2 y | Open label | Hydrocortisone | VGB: 150 mg/kg/d | Spasm cessation |
| Vigevano 1997 (43) | 42 | 2-9 mo | Open label | ACTH | VGB: 100-150 mg/kg/d | Spasm cessation |
| Appleton 1999 (44) | 45 | 1-20 mo | Double blind | Placebo | VGB: 50 - 150mg/kg/d | Spasm cessation |
| Elterman 2001 (45), Elterman 2010 (46) | 142 | <2 y | Single blind | 2 doses of VGB | 100-148 mg/kg/d; 18-36 mg/kg/d | Spasm cessation |
| Askalan 2003 (47) | 9 | 3 – 16 mo | Single blind | ACTH | 100-150 mg/kg/d | Spasm cessation |
| Lux 2004 (48), Lux 2005 (49) Darke 2010 (37) | 107 | 2-12 mo | Open label | ACTH/MP | Up to 150 mg/kg/d | Spasm cessation (2 weeks, 1 and 4 years) VABS (1 and 4 years) |
| *Other supportive studies* | | | | | | |
| Chiron 1991 (50) | 70 | | Prospective | None | | Spasm cessation |
| Aicardi 1996 (51) | 250 | | Retrospective | None | Mean: 99 mg/kg/d | Spasm cessation |
| Granstrom 1999 (52) | 42 | | Prospective | None | 50 – 100 mg/kg/d | Spasm cessation |
| Antoniuk 2000 (53) | 70 | NS | Retrospective | ACTH, Pred, VPA, NZP | NS | Spasm cessation |
| Ibrahim 2010 (54) | 56 | NS | Prospective | ACTH | Up to 150 mg/kg/d | Spasm cessation |

ACTH: adrenocorticotrophic hormone; MP: methylprednisolone; NS: not specified; NZP: nitrazepam; Pred: prednidolone; VABS: Vineland adaptive behaviour scale; VGB: vigabatrin; VPA: valproate

**Chiron C et al. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res 1997; 26: 389-95;**
**Description and Methods**: In order to compare vigabatrin to oral steroids, a prospective randomized multicenter study was implemented using both drugs as monotherapy in newly diagnosed patients with infantile spasms and tuberous sclerosis. Eleven infants received vigabatrin (150 mg/kg per day) and 11 hydrocortisone (15 mg/kg per day) for 1 month. Spasm free patients continued vigabatrin or progressively stopped hydrocortisone in 1 month, non-responders were crossed to the other drug for a new 2 month-period.

**Results**: All vigabatrin patients (11/11) were spasm-free versus 5/11 hydrocortisone infants. Seven patients were crossed to vigabatrin (six for inefficacy, one for adverse events) and became also totally controlled. Mean time to disappearance of infantile spasms was 3.5 days on vigabatrin versus 13 days on hydrocortisone.

**Vigevano et Cilio. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia 1997; 38: 1270-4;**
**Description and Methods**: To compare the efficacy and tolerability of vigabatrin (VGB) and adrenocorticotrophic hormone (ACTH) as first-line therapy in infantile spasms. Forty-two infants (22 males, 20 females) aged 2-9 months with newly diagnosed infantile spasms, were included in the trial. Patients were randomized to receive VGB 100-150 mg/kg/day or Depot ACTH 10 IU/day. The alternative drug was given if spasms were not controlled within 20 days or in cases of intolerance to initial therapy. Twenty-three patients (7 cryptogenic, 16 symptomatic) received VGB as first-line therapy; 19 patients (8 cryptogenic, 11 symptomatic) received ACTH.
**Results**: Cessation of spasms was observed in 11 (48%) of the patients randomized to VGB and in 14 (74%) of those randomized to ACTH. Response to VGB was observed within 1-14 days, but two-thirds of patients (7/11) responded within 3 days. In the group treated with VGB, side effects such as drowsiness, hypotonia and irritability were observed in 13% of patients, compared with 37% in the group treated with ACTH. VGB was more effective than ACTH as treatment for cerebral malformations or tuberous sclerosis, whereas ACTH proved more effective in perinatal hypoxic/ischemic injury. The efficacy of the two drugs was similar in cryptogenic cases. During the second phase, the alternative drug was given to the resistant patients. Spasms ceased in 2 of 5 patients treated with VGB and in 11 of 12 patients treated with ACTH. After 3 months, relapses of spasms were observed in 6 patients treated with ACTH and in 1 treated with VGB.

**Appleton RE et al. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia 1999; 40: 1627-33;**
**Description and Methods**: This prospective, randomised, and placebo-controlled trial of VGB in infantile spasms was considered to be justified and feasible to confirm or refute these previous findings. Forty children with newly diagnosed infantile spasms received either VGB or placebo for 5 days in a double blind, placebo-controlled, parallel-group study, after which all the infants continuing in the study were treated openly with VGB for a minimum of 24 weeks.
**Results**: Compared with baseline, at the end of the double-blind phase, the patients treated with VGB had a 78% (95% confidence interval, 55-89%) reduction in spasms compared with 26% (-56-65%) in the group treated with placebo. Seven VGB-treated patients and two placebo-treated patients were spasm free on the final day of the double-blind period. At the end of the study, 15 children (38% of the original 40 patients or 42% of the 36 patients who entered the open phase) were spasm free with VGB monotherapy.

**Elterman RD, Shields WD, Mansfield KA, Nakagawa J; US Infantile Spasms Vigabatrin Study Group. Randomized trial of vigabatrin in patients with infantile spasms. Neurology 2001; 57: 1416-21;**
**Elterman RD et al. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. J Child Neurol 2010; 25: 1340-7;**
**Description and Methods**: The authors evaluated the efficacy and safety of vigabatrin in children with recent-onset infantile spasms. This 2-week, randomized, single-masked, multicenter study with a 3- year, open-label, dose-ranging follow-up study included patients who were younger than 2 years of age, had a diagnosed duration of infantile spasms of no more than 3 months, and had not previously been treated with adrenocorticotropic hormone, prednisone, or valproic acid. Patients were randomly assigned to receive low-dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Treatment responders were those who were free of

infantile spasm for 7 consecutive days beginning within the first 14 days of vigabatrin therapy (confirmed by video-electroencephalogram)**.**
**Results**: Overall, 32 of 142 patients who were able to be evaluated for efficacy were treatment responders (8/75 receiving low-dose vigabatrin vs 24/67 receiving high doses). Response increased dramatically after approximately 2 weeks of vigabatrin therapy and continued to increase over the 3-month follow-up period. Time to response was shorter in those receiving high-dose versus low-dose vigabatrin and in those with tuberous sclerosis versus other etiologies. During follow-up (up to 3 years), 39 of 171 (23%) subjects relapsed; 28 of 39 (72%) regained spasm freedom.

**Askalan R et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. J Child Neurol 2003; 18: 165-70;**
**Description and Methods**: The objective of this study was to compare the efficacy of corticotropin (ACTH) versus vigabatrin in treating infantile spasms. Patients with infantile spasms were included in the study if they were 3 to 16 months old, had hypsarrhythmia, and had no previous treatment with vigabatrin or corticosteroids. Patients were stratified based on etiology (idiopathic or symptomatic) and then randomized between the ACTH and vigabatrin treatment groups for 2 weeks. Patients were considered responders if spasms and hypsarrhythmia resolved. Nine patients were included in the study.
**Results**: Three patients received ACTH, one of whom was a responder. Six patients received vigabatrin, three of whom were responders. The small number of infants in this pilot study is insufficient to determine which of the two drugs is more effective. However, the following trends were identified: vigabatrin may be more effective for patients with symptomatic infantile spasms.

**Lux AL et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 2004; 364: 1773–8;**
**Lux AL et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol 2005; 4: 712–17;**
**Darke K et al.; Trial steering committee on behalf of participating investigators. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomized trial. Arch Dis Child 2010; 95: 382-6;**
**Description and Methods**: The United Kingdom Infantile Spasms Study (UKISS) showed that absence of spasms on days 13 and 14 after randomisation was more common in infants allocated hormonal treatments than vigabatrin. At 12-14 months, those with no identified aetiology allocated hormonal treatment had better development. However, epilepsy outcome was not affected by treatment allocated. Infants in UKISS were followed up blind to treatment allocation at a mean age of 4 years using the Vineland Adaptive Behaviour Scales (VABS) and an epilepsy questionnaire.
**Results**: 9 of 107 enrolled infants had died. 77 were traced and consented to take part. The median (quartile) VABS scores were 60 (42, 97) for the 39 allocated hormonal treatment and 50 (36, 67) for the 38 allocated vigabatrin. For those with no identified aetiology, VABS scores were 96 (52, 102) for the 21 allocated hormonal treatment and 63 (37, 92) for the 16 allocated vigabatrin. The proportions in each treatment group with epilepsy were similar. For all 77 infants, development and epilepsy outcomes were not significantly different between the two treatment groups. The better development seen at 14 months in those with no identified aetiology allocated hormonal treatment was seen again at 4 years in this study.

**Chiron C et al. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991; 6(Suppl 2): S52-9;**

**Description and Methods**: Seventy children, including 47 infants, with intractable infantile spasms were entered into an open study with vigabatrin as add-on therapy to the usual anticonvulsant treatment. All were resistant to previous treatments, including corticosteroids (43 patients), carbamazepine, benzodiazepines, and sodium valproate.
**Results**: Two children withdrew from the study because of intolerance to vigabatrin (hypotonia or hypertonia) before evaluation of efficacy could be made. Of the remaining 68 children, 29 (43%) showed complete suppression of spasms. Forty-six children had a greater than 50% reduction in spasms. The best response was observed in those with tuberous sclerosis (12/14 compared with 12/18 with symptomatic infantile spasms of other origin and 22/36 with cryptogenic infantile spasms). Following the initial response to treatment of these patients (n = 68), a long-term response was confirmed in 75% of children with symptomatic infantile spasms and 36% of children with cryptogenic infantile spasms. In eight children, all other anticonvulsant medication could be definitively withdrawn. Tolerability appeared excellent, with 52 of 70 patients reporting no side effects. Somnolence, hypotonia, weight gain, excitation, and insomnia were the most common problems at the beginning of the study and were usually transient.

**Aicardi J et al. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. Sabril IS Investigator and Peer Review Groups. Epilepsia 1996; 37: 638-42;**
**Description and Methods**: The efficacy and tolerability of vigabatrin (VGB) as an add-on therapy in the treatment of infantile spasm (IS) prompted physicians to explore its use as the first drug in this seizure type. This retrospective study included 250 infants diagnosed with IS. Of this infant population, 192 infants were considered to have classic IS and had received VGB as their first treatment for the spasms.
**Results**: Initial suppression of spasms was obtained in 68% of infants with a median time to response of 4 days at an average VGB dose of 99 mg/kg/day. The best response was seen in those infants with tuberous sclerosis (96% response) and in those younger than 3 months at onset of spasms (90% response). Of these infants, 43 (22%) of 192 subsequently had other types of seizures, and a recurrence of infantile spasms occurred in 28 (21%) of 131 responders. At the end of this study, 96 of 192 infants who could be evaluated were seizure free with VGB monotherapy.

**Granström ML et al. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. Epilepsia 1999; 40: 950-7;**
**Description and Methods**: The efficacy of a protocol consisting of vigabatrin (VGB) as the first and adrenocorticotropic hormone (ACTH) or valproate (VPA) as the second drug was studied in the treatment of newly diagnosed infantile spasms (IS) during 1994 to 1997 in a population-based design. Only total disappearance of the spasms with a minimal duration of 1 month was accepted as a response.
**Results**: Altogether 42 infants, 10 with cryptogenic and 32 with symptomatic etiology, were treated. Eleven (26%) responded to VGB, five (50%) with cryptogenic, and six (19%) with symptomatic etiology; 91% of infants responded to a dose of 50-100 mg/kg/day, and 82% of them within 1 week. ACTH was offered in combination with VGB to 22 and VPA to four infants for whom VGB failed. Eleven responded to ACTH and one to VPA. In total, 26 (62%) infants responded to the treatment protocol; all (100%) with cryptogenic etiology and 16 (50%) with symptomatic etiology. ACTH treatment was associated with more severe side effects than VGB or VPA.

**Antoniuk SA et al. [West syndrome: clinical and electroencephalographic follow up of 70 patients and response to its treatment with adrenocorticotropic hormone, prednisone, vigabatrin, nitrazepam and valproate]. Arq Neuropsiquiatr 2000; 58: 683-90;**
**Description and Methods**: This retrospective study assessed the outcome of the criptogenic and symptomatic forms of West syndrome and evaluated the efficacy of adrenocorticotropic hormone, vigabatrin, prednisone, valproate and nitrazepam in the spasms control.

**Results**: Seventy patients were followed up by 2 years. Twelve (17%) were criptogenics and 58 (83%) symptomatics. In criptogenic group significantly more patients were in regular school classes and with normal motor development, better control of seizure, less tendency to evoluate to Lennox Gastaut syndrome and 83. 3% had control of spasms (72.4% of patients from symptomatic group had control of spasms). Adrenocorticotropic hormone and vigabatrin were the most efective drugs, with 68.75% and 60% of spasms control, respectivelly, when used as first line of therapy and 75% and 50%, respectivelly, as second line of therapy.

**Ibrahim S et al. Clinical profile and treatment of infantile spasms using vigabatrin and ACTH--a developing country perspective. BMC Pediatr 2010; 10:1;**
**Description and Methods**: This study describes the comparison of their efficacy in a large series of patients with infantile spasms from Pakistan. All patients with infantile spasms who presented to Aga Khan University Hospital, Karachi, Pakistan from January, 2006 to April, 2008 were included in this study. Inclusion criteria were clinical symptoms of infantile spasms, hypsarrythmia or modified hyparrythmia on electroencephalography, at least six months of follow-up period and receipt of any of the two drugs mentioned above. The type of drug distribution was random according to the availability, cost and ease of administration.
**Results**: Fifty six cases fulfilled the inclusion criteria. Mean age at onset of seizures was 5 +/- 1.4 months. 64.3% cases were identified as symptomatic while 19.6% were cryptogenic and 16.1% were idiopathic. Eighteen patients received ACTH while 38 patients received Vigabatrin as first line therapy. Initial response to first line therapy was similar (50% for ACTH and 55.3% for Vigabatrin). Overall, the symptomatic and idiopathic groups responded better to Vigabatrin. The relapse rate was higher for ACTH as compared to Vigabatrin (55.5% vs. 33.3%) when considering the first line therapy.

There is one systematic review (Hancock et al., 2008) comparing the effects of single pharmaceutical therapies used to treat infantile spasms in terms of spasm control, resolution of the EEG, relapse rates, psychomotor development, subsequent epilepsy, side effects and mortality. Five of the studies included evaluated vigabatrin (Chiron et al., 1997; Appleton et al., 1999; Elterman et al., 2001; Askalan et al., 2003; Lux et al., 2004). The effect sizes for the various outcomes reported in the vigabatrin studies are provided in Table 2. The authors of the review commented on the paucity of controlled studies in West syndrome, on the small sample sizes employed, and on the poor methodological quality of the studies.

**Table 2.** Treatment with vigabatrin in studies on infantile spams

| Study | Outcome | Trials | Odds ratio | Mean difference |
|---|---|---|---|---|
| Vigabatrin vs placebo | Cessation of spasms | 1 | 4.05 [0.93 – 17.52] | |
| | Resolution of hypsarrhythmia | 1 | 2.36 [0.10 – 54.60] | |
| | Patients remaining spasm-free | 1 | 8.23 [0.81 – 84.07] | |
| Vigabatrin vs hydrocortisone | Cessation of spasms | 1 | 13.8 [2.2 – 86.4] | |
| | Time to cessation | 1 | | -8.8 [-19.22 – 1.62] |
| Vigabatrin vs ACTH or MP | Cessation of spasms | 3 | 0.42 [0.21 – 0.80] | |
| | Resolution of hypsarrhythmia | 3 | 0.38 [0.15 – 0.99] | |
| | Seizure recurrence at follow-up | 3 | 0.69 [0.36 – 1.32] | |

*Studies in partial epilepsy*

Three randomised clinical trials have evaluated the efficacy of vigabatrin for the treatment of partial epilepsy in children (Table 3). One compared vigabatrin to placebo and two vigabatrin to carbamazepine. Several earlier studies used a single-blind, fixed-sequence placebo-controlled design. In these studies, patients were evaluated for a fixed duration during which placebo was administered and then moved to vigabatrin and evaluated for a further period of identical or longer duration. Such studies were used to support the original new drug application for vigabatrin use in epilepsy. In addition, a number of other randomised clinical trials have been performed in mixed populations of adults and children, for which no data for the paediatric subgroup were presented. These studies are listed in Table 3 but not discussed in more detail (by the Rapporteur). Finally, a number of supportive non-randomised or non-comparative studies performed in paediatric populations are shortly described where they provide further information and include at least thirty patients ("Other supportive studies"). Main methods of the studies are presented in Table 3. Results of each study are briefly summarized below."

**Table 3**. Clinical studies of vigabatrin in the treatment of partial epilepsy in paediatric populations

| Study | N | Age range | Design | Comparator | Daily dose of VGB | Primary end-point |
|---|---|---|---|---|---|---|
| Randomised clinical trials in paediatric populations | | | | | | |
| Chiron 1996 (55) | 28 | 1.5 – 18.35 years | DB, E-W | Placebo | NS | Retention in withdrawal phase |
| Zamponi 1999 (56) | 70 | 6 mo – 13 yr | Open-label | Carbamazepine | 50-60 mg/kg/d | Treatment failure |
| Sobaniec 2005 (57) | 64 | 5-17 years | Open-label | Carbamazepine | 50 mg/kg bid | Reduction in seizure frequency by class |
| Fixed-sequence placebo-controlled studies | | | | | | |
| Luna 1989 (58) | 61 | | SB, FS | Placebo | | Reduction in seizure frequency ≥50% |
| Dulac 1991 (59) | 66 | | SB, FS | Placebo | | Reduction in seizure frequency ≥50% |
| Herranz 1991 (60) | 20 | 2 months – 18 years | SB, FS, DI | Placebo | 1, 1.5 & 2 g/d | Response rate, seizure freedom rate |
| Dalla Bernardina 1995 (61) | 46 | | SB, FS-DI | Placebo | 40 – 80 mg/kg/d | Response rate, seizure freedom rate |
| Randomised clinical trials in mixed populations of children and adults | | | | | | |
| Gram 1985 (62) | 21 | | Double-blind | Placebo | | Reduction in seizure frequency by class |
| Loiseau 1986 (63) | 19 | 10 – 58 years | Double-blind | Placebo | 1.5 g/d | Reduction in seizure frequency |
| Tassinari 1987 (64) | 31 | 10 – 58 years | Double-blind | Placebo | 2 – 3 g/d | Reduction in seizure frequency |
| Grünewald 1994 (65) | 45 | 15 – 61 years | Double-blind | Placebo | 1.5 g/d | Seizure frequency; cognition |
| Chadwick 1999 (66) | 459 | 12 – 65 years | Double-blind | Carbamazepine | 2 g/d | Retention on treatment |
| Brodie 1999 (67) | 215 | 12 – 75 years | Double-blind | Valproate | 2 – 4 g/d | Reduction in seizure frequency ≥50% |
| Lindberger 2000 (68) | 102 | 12 – 65 years | Double-blind | Gabapentin | 0.9 – 1.8 g/d | Seizure freedom rate |
| Sivenius 1987 (69) | 75 | 15 -55 years | Double-blind | 2 doses of VGB | 1.5 g/d & 3 g/d | Seizure frequency |
| Other supportive studies | | | | | | |
| Uldall 1991 (70) | 27 | | Prospective | None | | Reduction in seizure frequency by class |
| Gibbs 1992 (71) | 43 | | Retrospective | None | | Reduction in seizure frequency ≥50% |
| Gherpelli 1997 (72) | 37 | 6 months – 18 years | Prospective | None | 19 – 111 mg/kg/d | Reduction in seizure frequency by class |
| Coppola 1997 (73) | 52 | 4 months – 23 years | Prospective | None | Up to 50 mg/kg/d | Reduction in seizure frequency by class |
| Nabbout 1997 (74) | 175 | 1 week – 19 years | Patient registry | None described | NS | Response rate, seizure freedom, relapse |

DB: double-blind; DI; dose increasing; E-W: enrichment-withdrawal; FS: fixed sequence; NS: not specified; SB: single blind; VGB: vigabatrin

**Chiron C et al. Vigabatrin withdrawal randomized study in children. Epilepsy Res 1996; 25: 209-15;**

**Description and Methods:** This study used an enrichment withdrawal-randomisation design in order to evaluate the ability of vigabatrin to reduce seizure frequency in children with epilepsy, compared to placebo. Patients previously treated with vigabatrin who had experienced a partial response to the drug (<50 % reduction in seizure frequency) were included.

**Results:** Twenty-eight patients aged 1.5-18.5 years and having partially responded to VGB, prescribed in an open study for refractory epilepsy, were included. Patients were randomized to VGB (continued) or placebo (VGB blindy stopped in 3 weeks) for 2 months and seizure

frequency was compared to the prerandomization period. More than 50% increase in seizure frequency induced drop-out. Fifteen patients received VGB, 13 others placebo, with the same clinical characteristics in both groups. The patients remaining in the study (primary efficacy endpoint) were more numerous on VGB (93%) than on placebo (46%) ($P < 0.01$) and seizure frequency (secondary endpoint) was lower on VGB than placebo ($P < 0.05$). The same results were observed in a subgroup of partial epilepsies. No status epilepticus was observed when withdrawing VGB and all patients returned to baseline status by reintroducing VGB.

**Zamponi et al. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. Arch Neurol 1999; 56: 605-7;**
**Description and Methods:** To compare vigabatrin with carbamazepine as monotherapy in newly diagnosed children with partial epilepsy in order to evaluate the efficacy and tolerability of both drugs. Design: Open and randomized with a 2-year follow-up period. Seventy children with newly diagnosed partial epilepsy were treated with vigabatrin (38 patients) or carbamazepine (32 patients). Vigabatrin, 50 to 60 mg/kg per day, or carbamazepine, 15 to 20 mg/kg per day, split into twice-a-day doses. The efficacy and tolerability of vigabatrin were compared with those of the standard treatment (carbamazepine) for this patient group.
**Results**: The efficacy of vigabatrin and carbamazepine was similar, with the suggestion of a better side effect profile with vigabatrin. More studies are needed to evaluate other issues of concern, such as the cognitive and behavioral adverse effects of antiepileptic drugs, to determine the most suitable therapy.

**Sobaniec et al. A comparative study of vigabatrin vs. carbamazepine in monotherapy of newly diagnosed partial seizures in children. Pharmacol Rep 2005; 57: 646-53;**
**Description and Methods:** The objective of this study is to evaluate the safety, efficacy and EEG effects of initial VGB monotherapy compared with initial CBZ monotherapy in children with newly diagnosed epilepsy.
**Results**: We present results of a prospective, outpatient and open study. Twenty-six children with partial epilepsy treated with VGB and 28 patients treated with CBZ were studied. The evaluation of the efficacy of the two drugs did not reveal any significant differences. Very good (reduction > 75%) seizure control was achieved in 22 out of 26 patients (84.6%) in the VGB group. One patient had a 50-75% decrease of seizures (good effect), similarly one child had a 25-50% reduction of seizures (mild effect). In two patients, we observed increased seizures (myoclonic jerks). Very good seizure control was achieved in 17 out of 28 patients (60.7%) in the CBZ group. Good seizure control was achieved in 5 out of 28 patients (17.8%) and mild control was seen in two children. No improvement was observed in 4 (14%) of the patients.

**Luna D et al. Vigabatrin in the treatment of childhood epilepsies: a single-blind placebo-controlled study. Epilepsia 1989; 30: 430-7;**
**Description and Methods:** Sixty-one pediatric patients (12-229 months of age) with refractory epilepsy were treated with vigabatrin [gamma-vinyl GABA (GVG)] in a 16-week, single-blind, add-on, placebo-controlled trial.
**Results**: Twenty-three patients (38%) showed a reduction of more than 50% in seizure frequency; 12 patients (20%) experienced a seizure increase; and the remaining 26 did not show significant differences between placebo and GVG treatment. Among the 216 patients who entered the long-term phase after having experienced more than 50% decrease in seizure frequency, 14 continued with the same degree of improvement after 2-11 months of follow-up (mean 7.7). GVG was particularly efficient in cryptogenic partial epilepsy. Conversely, nonprogressive myoclonic epilepsy tended to be aggravated. Agitation was the most commonly observed side effect, mainly at onset of therapy in mentally retarded patients, but was easily reversed by dose reduction.

**Dulac O et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; 6(Suppl 2): S30-7;**
**Description and Methods:** Sixty-six children with various types of severe drug-resistant epilepsy were entered into a long-term, dose-rising study of vigabatrin after a 4-week run-in placebo period. All the children were receiving one to three other antiepileptic drugs, the doses of which were not changed during the 6-month dose titration phase.
**Results**: Following the introduction of vigabatrin, 11 patients became seizure free, and 28 responded with a greater than 50% reduction in seizure frequency. The following types of epilepsy responded favorably in order of decreasing efficacy: cryptogenic and symptomatic partial epilepsy, other symptomatic generalized epilepsy, and Lennox-Gastaut syndrome. However, three of nine patients with myoclonic epilepsy showed an increase in seizure frequency. Optimal responses were found with vigabatrin doses of 40 to 80 mg/kg/day, although no significant adverse effects were noted with doses of higher than 100 mg/kg/day. Thirty-eight responders continued on vigabatrin, 19 of whom have been treated for more than 1 year, with generally good efficacy. As a result of discontinuing concomitant antiepileptics, six patients are on monotherapy with vigabatrin, four of whom are seizure free. Vigabatrin tolerability was good, with 39 of 66 children reporting no adverse effects. Hyperkinesia was reported in 17 patients (26%), and two had to drop out of the study. All these patients had a history of hyperkinesia or mental retardation. In patients in whom vigabatrin dose was reduced because of hyperkinesia, a dose increase could later be instituted without recurrence of symptoms. There was no change in neurologic examination and no drug-related abnormalities in clinical laboratory data.

**Herranz JL et al. Dose-response study of vigabatrin in children with refractory epilepsy. J Child Neurol 1991; Suppl 2: S45-51;**
**Description and Methods:** Twenty children aged 2 months to 18 years were included in a dose-response study of vigabatrin as add-on therapy to preexisting antiepileptic drugs (up to two per patient). All children had severe refractory epilepsy: partial seizures with or without secondary generalization in 19, and myoclonic seizures in one. After a 2-month observation period and a 1-month add-on placebo period, a fixed dose of add-on vigabatrin was given for 2 months: 1, 1.5, or 2 g/day, according to body weight (mean dose, 60 mg/kg/day).
**Results**: Three patients (15%) became seizure free, and nine (45%) showed a 50% to 99% reduction in seizure frequency. In the 17 patients whose seizures were not totally suppressed, vigabatrin dose was increased for a further 2 months, and in 7 patients who still showed less than 50% reduction in seizure frequency, vigabatrin dose was increased again. Efficacy appeared unchanged by these higher doses. During a 9-month follow-up phase, no tolerance to the effects of vigabatrin was observed, with three children seizure free and 13 (65%) reporting a 50% to 99% reduction in seizure frequency. During the study, adverse effects were recorded in three children (15%), namely drowsiness, constipation, fatigue, and apathy. These effects were generally transient, being observed during the dose-modification phase and disappearing either spontaneously or on reduction of vigabatrin dose. Clinical and laboratory tolerability to vigabatrin appeared to be very good, with no patients having withdrawn from the study because of side effects. A slight reduction in red blood cell count and hemoglobin levels was noted but was of doubtful clinical significance. There was also a slight, nonsignificant decrease in phenytoin plasma levels.

**Dalla Bernardina B et al. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. Epilepsia 1995; 36: 687-91;**
**Description and Methods:** The efficacy and tolerability of vigabatrin (VGB) in children with refractory partial epilepsy were assessed in a single-blind, add-on, fixed-sequence, placebo-controlled trial. After 1-month observation, the patients entered a 7-month treatment period that involved administration of placebo for 1 month followed by VGB at the initial dosage of 40 mg/kg/day, to be increased to 60 and 80 mg/kg/day at 2-month intervals if seizures persisted.
**Results**: Of the 46 children enrolled in the study, 7 dropped out prematurely due to lack of efficacy of the drug (n = 6) or increased seizure frequency (n = 1). In 11 patients who either

became seizure-free (n = 3) or improved markedly (n = 8), treatment was completed at a dose < 80 mg/kg/day. The average number of seizures per month in the 39 patients who completed the study decreased from 97 during placebo to 21, 12, and 9 after 2, 4, and 6 months of VGB treatments respectively ($p < 0.0001$ at each time). Response to VGB remained statistically significant when dropouts were included in the evaluation. The number of patients who had > 50% reduction in seizure frequency after 2, 4, and 6 months was 28, 33, and 35, respectively. Eight patients became seizure-free during the last 2 months of VGB treatment (3 at 40, 3 at 60, and 2 at 80 mg/kg/day, as compared with none during placebo treatment). Serum levels of associated antiepileptic drugs (AEDs) showed no significant changes, except for serum phenytoin (PHT) concentration, which significantly ($p < 0.01$) decreased after VGB treatment. Increased appetite and sedation were observed in 17 and 11 % of cases, respectively.

**Gram L et al. Gamma-Vinyl GABA: a double-blind placebo-controlled trial in partial epilepsy. Ann Neurol 1985; 17: 262-6;**
**Loiseau P et al. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia 1986; 27: 115-20;**
**Tassinari CA et al. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987; 44: 907-10;**
**Grünewald RA et al. Effects of vigabatrin on partial seizures and cognitive function. J Neurol Neurosurg Psychiatry 1994; 57: 1057-63;**
**Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. Lancet 1999; 354: 13-9;**
**Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. Epilepsy Res 1999; 34: 199-205;**
**Lindberger M et al. Gabapentin versus vigabatrin as first add-on for patients with partial seizures that failed to respond to monotherapy: a randomized, double-blind, dose titration study. GREAT Study. Epilepsia 2000; 41(10): 1289-95;**
**Sivenius MR et al. Double-blind dose reduction study of vigabatrin in complex partial epilepsy. Epilepsia 1987; 28: 688-92**
The eight studies listed above, published in years 1985–2000, are randomized clinical trials performed in mixed populations of children and adults without subgroup analyses for children. The mean age of subjects included in these studies seems to vary between 27-37 years, and number of children included is typically low (e.g., 6 children <18 years in Loiseau et al., 1986.) For some methodological details, see Table 3. These studies are not reviewed in more detail by the Rapporteur. The MAH did provide a short description of each of these studies as well.

**Uldall P et al. Vigabatrin in pediatric epilepsy--an open study. J Child Neurol 1991; Suppl 2: S38-44;**
**Description and Methods:** In order to assess the long-term effect and safety of vigabatrin in patients with severe epilepsy, an open, add-on, dose-ranging study was initiated.
**Results**: To date, 27 children with partial epilepsy, two with generalized epilepsy, two with Lennox-Gastaut syndrome, and one with non-classifiable epilepsy have been enrolled in the trial. Fifty-four percent of patients have experienced a greater than 50% reduction in seizure frequency, and four patients have become seizure free. A significant reduction in seizures was noted across the patient population, although patients who were recorded as seizure free at 3 and 6 months did suffer some recurrence of seizures. However, when seizures recurred, they did so at much lower frequency than recorded at the start of the study. Thirteen patients (39%) reported adverse events attributable to vigabatrin; one was immediately withdrawn from the study, and six had their vigabatrin dose reduced. No physiologic effects were noted on normal growth or clinical physical examination.

**Gibbs JM et al. Vigabatrin in intractable childhood epilepsy: a retrospective study. Pediatr Neurol 1992; 8: 338-40;**
**Description and Methods:** The effects of vigabatrin were studied over a 6-month period in 43 patients with intractable epilepsy.
**Results**: Children with complex partial seizures, with or without secondary generalization, responded best with more than one-half achieving a greater than 50% reduction; generalized tonic-clonic seizures also improved but there was no significant change in absence or myoclonic seizures. Four patients are seizure-free on monotherapy with vigabatrin.

**Gherpelli JL et al. Vigabatrin in refractory childhood epilepsy. The Brazilian Multicenter Study. Epilepsy Res 1997; 29: 1-6;**
**Description and Methods:** Children, 47, with various types of severe drug-resistant epilepsy were entered into a prospective, add-on, open trial with vigabatrin. Patients with West syndrome and idiopathic generalized epilepsies were excluded.
**Results**: Seven children had the drug withdrawn, five because of increase in seizure frequency and two because of adverse effects. Drug efficacy, measured according to seizure type, showed a 100% decrease in seizure frequency in 18.6% of partial seizures and 17.3% of the generalized seizures. There was a higher than 50% decrease in 39.5% of partial and 60.8% of generalized seizures, and less than 50% decrease or increase in seizure frequency in 41.8% and 21.8% of partial and generalized seizures, respectively. Vigabatrin mean dosage during phase 3 was 63.6 mg/kg per day (S.D. = 30.5), ranging from 19.3 to 110.5 mg/kg per day. Parametric statistical analysis (Student's t-test) of seizure frequency between phases 1 and 3 showed a significant decrease in seizure frequency for partial ($P = 0.022$), and generalized seizures ($P < 0.0001$). Drug-related adverse effects were observed in 18/47 cases (38.3%), consisting mainly of irritability, hyperactivity, dizziness, somnolence and gastrointestinal symptoms.

**Coppola G et al. Vigabatrin as add-on therapy in children and adolescents with refractory epilepsy: an open trial. Brain Dev 1997; 19: 459-63;**
**Description and Methods:** Seventy-seven children and adolescents with drug-resistant epilepsies received vigabatrin as add-on therapy for a median of 18 months (range 4-36 months) at a dose of 50 mg/kg/day divided in two doses; patients with spasms were given a maximum dose of 100 mg/kg/day.
**Results**: In 23 patients (29.9%), seizure frequency decreased by 50-100% and in 12 patients (15.6%) by 25-50%. The number of seizures remained unchanged in 34 patients (44.1%) and increased in seven (9.1%). Vigabatrin was most effective in cryptogenic and symptomatic partial seizures (39% and 43%, respectively), and in infantile spasms (25%). Adverse events occurred in 20 patients (26%), though they were generally mild and transient.

**Nabbout RC et al. Vigabatrin in partial seizures in children. J Child Neurol 1997; 12: 172-7;**
**Description and Methods:** Patients with partial seizures aged 1 week to 19 years (n = 175) were included in several prospective vigabatrin studies.
**Results**: A decrease in seizure frequency of over 50% was achieved in 70% of patients, with 30% becoming seizure free, and only 6% experiencing an increase. Tuberous sclerosis gave the best response (85%), tumors the lowest (45%), the usual figure for other causes being 70%. Patients with malformations were the most likely to experience seizure increase. Regarding topography of focus, the lowest rate of seizure-free patients was in rolandic foci. Early treatment produced better results. Infants experienced the highest rate of response, but also of relapse, the latter occurring mainly between 6 months and 1 year. The incidence of loss of efficacy depended on etiology and topography of focus, tumors and frontal foci having the highest risk. Occurrence of new seizures was more frequent in young patients with tuberous sclerosis, the third experiencing status epilepticus. Vigabatrin monotherapy could only be achieved in 33% of seizure-free patients, reduction of co-medication being a risk of relapse and of further intractability.

In conclusion, there is no new efficacy information leading to a change in indication or dose recommendation or in addition of information in section 5.1. Paediatric information provided in the SmPC section 4.2 and PL section 3. should, however, be clarified and presented according to the SmPC guideline and the latest QRD template.

Safety

*Clinical trials and postmarketing safety data*

To evaluate safety of vigabatrin treatment in paediatric populations the MAH reviewed data from clinical trials and performed a search in the pharmacovigilance database to retrieve all cases, reported since the vigabatrin launch until 31 May 2011, in patients aged less than 18 years and exposed to vigabatrin. In addition, published safety studies performed with vigabatrin in children, which were provided in Periodic Safety Update Reports (PSURs), were retrieved.

Following the present Art. 45 evaluation of data provided by the MAH, the product information should be amended to include cases with the following undesirable effects (both paediatric and adult cases were observed): Blood and lymphatic system disorders / Anaemia (frequency: common) and Musculoskeletal and connective tissue disorders / Arthralgia (frequency: very common).

*Literature references: General safety*

**Chiron C et al. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991; 6(Suppl 2): S52-9;**
**Dulac O et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; 6(Suppl 2): S30-7**
For summaries of Results including Safety of these two studies see sections Efficacy / Studies in West syndrome and Studies in partial epilepsy, respectively.

**Kankirawatana P et al. Vigabatrin therapy in infantile spasms. J Med Assoc Thai 2002; 85(Suppl 2): S778-83;**
**Description and Methods:** To determine the clinical outcome and side effects of vigabatrin (VGB) in the treatment of infantile spasms (IS) and its long-term outcome. All children with IS treated with vigabatrin were studied. Clinical data regarding age of onset, duration of IS before therapy started, recurrence of IS, types of seizures that relapse, clinical outcome and side effects were monitored.
**Results**: 36 children (17 girls, 19 boys) with IS participated in the study. The mean age of onset of IS was 115.55 +/- 67.3 days old (range, 15 to 300 days). Six were cryptogenic IS and 30 were symptomatic IS. The etiologies of symptomatic IS in this study were tuberous sclerosis, hypoxic ischemic encephalopathy (HIE)/periventricular leukomalacia, porencephaly, partial agenesis of corpus callosum, hemimegalencephaly, cortical dysplasia, and microcephaly. 66.67 per cent (24 of 36) of patients responded to VGB within a mean 2.95 +/- 2.25 days (range, 1 to 7 days). In those who responded to VGB, 3 patients developed recurrent IS within 69.3 +/- 46.7 days (range, 30 to 121 days). Five patients developed epilepsy with different types of seizure during long-term follow-up. The mean duration of subsequent epilepsy after cessation of IS was 16.4 months (range, 5 months to 3 years 10 months). The mean duration of follow-up was 2.74 years (range, 1.09 years to 5.76 years). 10 patients were successfully weaned off VGB after a mean IS free period of 22.5 +/- 5.5 months (range, 12 to 27 months). Transient drowsiness was seen in 4 patients. Three patients had transient abnormal sleep patterns and irritability. Visual field abnormalities were not found but difficult to assess fully in this study. VGB therapy has a high response rate for the control of IS and is well tolerated in most children. All patients who responded to VGB and were spasm free for more than one year were successfully weaned off

VGB therapy. Because serious side effects such as visual field abnormalities are difficult to monitor, the authors propose that VGB could be withdrawn or switched to another AED after a spasm-free period of more than one year.

**Moraes MHP et al. Efficacy and tolerability of vigabatrin in West syndrome. Arquivos de Neuro-Psiquiatria 2005; 63(2B): 469-73;**
**Description and Methods:** To evaluate the safety and efficacy of vigabatrin (VGB) in the treatment of WS. Every patient diagnosed with WS seen at the pediatric epilepsy clinic and exposed to VGB was evaluated. Patients were interviewed according to a semistructured questionnaire and we analyzed gender, age, etiology (cryptogenic or symptomatic), associated diseases, age of seizure onset, neuroimaging findings, EEG prior and after VGB, use of other antiepileptic drugs, time for seizure control, electroretinogram, visual complaints, adverse events and family history of epilepsy.
**Results**: Twenty-three patients were evaluated, 16 boys, ages ranging from 1.25 years to 11.5 years (mean=5y3m). Sixteen (69.5%) patients were seizure free, five (22%) had partial seizure control and in two (8.5%) there was no improvement. Only one patient presented gabaergic retinopathy. Six (26%) patients presented adverse events: somnolence, aggressivity or retinopathy. Patients with seizure onset after 6 months of age presented better results after VGB introduction ($p<0.05$). There was no difference in seizure control according to duration of epilepsy before VGB treatment or etiology of the seizures ($p>0.05$). After VGB, no patient presented hipsarrhythymia and 50% had a normal EEG. Although VGB may be associated with serious adverse events such as gabaergic retinopathy, our results show that it should be considered in the treatment of WS.

**Turanli G et al. Vigabatrin in paediatric patients with refractory epilepsy. Turk J Pediatr 2006; 48(1): 25-30;**
**Description and Methods:** The efficacy and side effect profile of vigabatrin (VGB) in pediatric patients with intractable seizure disorder were studied by reviewing the database of a short-term video-EEG monitoring laboratory to screen patients with intractable epilepsy who were on VGB either alone or in combination for three months or more. The authors subsequently reviewed the medical records of the patients to abstract clinical information regarding age, sex, seizure type, epilepsy syndrome, efficacy and side effects of VGB.
**Results**: Of 111 patients, 75 (68%) were male and 36 (32%) female. Seizure onset was during the newborn period in 12 patients (11%), during the first year of life beyond the newborn period in 47 patients (42%), between 1-5 years in 23 patients (21%), and above five years in the remaining 29 patients (26%). Fifty-four patients (48.6%) had partial onset seizures with or without secondary generalization; 49 patients (44.1%) had primary generalized seizures; 8 patients (7.2%) had two or more types of seizure. Fifty-three percent of patients had mental retardation, and 35% had abnormal findings on physical/ neurological examination. Of 98 patients, 70 (71.4%) had abnormal magnetic resonance imaging (MRI) findings. Ninety-seven percent of patients had been on polytherapy before VGB was added to treatment. VGB reduced seizure frequency by at least 50% in 33.3% of patients with partial seizures, and in 30.6% of patients with primary generalized seizures. Six of the responders with partial seizures had complete resolution of their seizures. Most common side effects included visual field defects, increased appetite and obesity. Vigabatrin seems to be more effective in partial seizures in childhood intractable epilepsy. Patients should be closely monitored regarding side effects of VGB.

**Aurich-Barrera B et al. Paediatric Prescrition-Event Monitoring (PEM) and its role in risk management: Results of a modified PEM study on lamotrigine and vigabatrin. Drug safety 2006; 29: 911-1010 (Abs 112);**
**Description and Methods:** To determine whether there are differences in the adverse event profile of children and adults in the lamotrigine and vigabatrin Prescrition-Event Monitoring

studies. Data between 1991 to 1995, were stratified by age (<2 years, 2-11 years, 12-17 years and ≥18 years) and examined using summary statistics for, ADRs, reasons for stopping, deaths and followup information. Incidence densities were calculated for both paediatric (0-17 years) and adult (≥18 years) adverse event data, for the 1st month and 2nd to 6th months of treatment, to examine whether the adverse event rate was different in these 2 observation periods. Proportional Reporting Ratios (PRRs) and incidence rate ratios were calculated comparing children with adults within each drug, to identify possible differences in adverse events reported between children and adults ($p < 0.05$).
**Results**: The lamotrigine Prescrition-Event Monitoring cohort comprised 2,457 children and 7,379 adults; the vigabatrin cohort contained 3,196 children and 6,007 adults. In both studies a higher proportion of the ADRs in adults was reported. Anticonvulsant hypersensitivity syndrome was not reported. For both drugs the frequency and type of paediatric and adult adverse event signals differed. Stevens-Johnson syndrome was more commonly reported in children than adults taking lamotrigine (PRR 4.50; Chi-squared 4.81). In the vigabatrin study, psychiatric adverse event signals detected for children were general behavioural changes such as hyperactivity (PRR 4.46, Chi-squared 13.64), whereas for adults they were more specific events such as abnormal dreams (PRR 0.21, Chi-squared 4.37).

**Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. J Child Neurol 2007; 22: 1360-6;**
**Description and Methods:** Using a retrospective chart review of 130 patients, the authors compare major adverse events, weight and blood pressure changes, and unplanned medication changes associated with adrenocorticotropic hormone (ACTH) injections versus other antiepileptic drugs.
**Results**: Children treated with adrenocorticotropic hormone injections experienced significant short-term weight gain and blood pressure elevations, which were readily reversible with weaning off the drug. Twenty-three (23) percent of patients treated with ACTH (14 of 60), 15% of patients treated with vigabatrin (5 of 34) and 33% of patients treated with other antiepileptic drugs (6 of 18) experienced a major adverse event during treatment. Few patients overall required a change in medication due to intolerable side effects. Despite early changes in weight and blood pressure, short courses of high-dose natural adrenocorticotropic hormone are generally well tolerated with no increased major adverse events when compared to antiepileptic drugs in the treatment of infantile spasms.

**Camposano SE et al. Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile. Epilepsia 2008; 49: 1186-91;**
**Description and Methods:** To review the efficacy, cognitive outcome and safety profile in children treated with vigabatrin (VGB) for infantile spasms (IS) and partial epilepsies related to tuberous sclerosis complex (TSC) and other etiologies.
**Results**: Eighty-four children were treated with VGB, 68 of them were treated for IS, and 59 were treated for partial seizures (PS). Etiology (TSC or other) was the only predictive factor for IS control with VGB ($p < 0.0003$). IS control was achieved in 73% of children with TSC and 27% of children with other etiologies (combined 56%). Partial onset seizures were controlled in 34% of all children, (17% seizure free, 17% reduction in seizure frequency >50%) and no predictive factor was found. Shorter time from seizure onset to VGB treatment ($p < 0.027$) and longer total time on VGB ($p < 0.045$) was associated with better IQ-developmental quotient (DQ) outcome in children treated for IS, but not with IS control. Adverse events were seen in 13%. Electroretinogram and/or behavioral visual field (VF) testing was done in 52%. VGB was discontinued in one case due to abnormal electroretinogram (ERG) findings. VGB may improve cognitive outcome in the absence of complete IS control, but this finding is of uncertain clinical significance. VGB was well tolerated, and ophthalmologic side effects were uncommon.

**Cohen-Sadan S et al. Multicenter long-term follow-up of children with idiopathic West syndrome: ACTH versus vigabatrin. Eur J Neurol 2009; 16: 482-7;**
**Description and Methods**: Long-term follow-up of children with idiopathic West syndrome (WS) treated with adrenocorticotropic hormone (ACTH) or vigabatrin. Records of 28 normal magnetic resonance imaging (MRI) WS cases were reviewed for seizure development and cognitive outcome in relation to treatment type and lag.
**Results**: Average age at disease onset was 5.5 months, and average lag time to treatment was 25 days. Fourteen patients were treated with ACTH (eight early and six late), and 14 with vigabatrin (without delay). Response rates were 88% for ACTH and 80% for vigabatrin. Short-term outcomes for seizure cessation and electroencephalography normalization were identical between the groups. In the long-term, early ACTH treatment was better than the rest combined. Average follow-up time was 9 years. A normal cognitive outcome was achieved in 100% of the early-ACTH group, 67% of the late-ACTH group and 54% of the vigabatrin group ($P = 0.03$). Seizures subsequently developed in 54% of the vigabatrin group, in 33% of the late ACTH group, and 0% of the early ACTH group ($P < 0.05$). Idiopathic WS with normal MRI is associated with a good cognitive outcome. Early ACTH treatment, administered within 1 month, yields a better cognitive and seizure outcome than vigabatrin or late ACTH.

**Kwon YS et al. Combined treatment with topiramate and vigabatrin in idiopathic infantile spasms. Eur J Neurol 2009;16(S3): AbsP2430;**
**Description and Methods**: This study evaluated the efficacy and tolerability of combined treatment with topiramate and vigabatrin in 10 children with idiopathic infantile spasms.
**Results**: After the combined treatment of topiramate and vigabatrin, the patients were spasm-free and disappearance of hypsarrhythmia was observed. Seizure reduction was observed in a few patients. Lethargy, irritability, and sleep disturbance were observed as mild adverse events.

*Literature references: Visual field defect*

**Harding GFA et al. Vigabatrin; Its effect on the electrophysiology of vision. Documenta Ophthalmologica 2002; 104: 213-29;**
**Description and Methods**: Vigabatrin is known to induce visual field defects in approximately one third of patients treated with the drug. It is apparent from electrophysiological studies that the cause of this defect is at retinal level probably as a result of the build up of GABA. Paediatric patients treated with the drug at age 9 years or below cannot reliably perform visual field perimetry. To identify these patients a special VEP H-Stimulus has been developed to produce separate responses from central and peripheral field stimulation by alternating at slightly separate rates.
**Results**: Forty-five healthy children between ages 3 and 10 years have been used to develop a normal database. This technique has a sensitivity of 75% and a specificity of 87.5% in identifying the field defect and may be used in children with epilepsy from age 3 upwards.

**Harding GFA et al. Field-specific visual-evoked potentials: Identifying field defects in vigabatrin-treated children. Neurology 2002; 58: 1261-5;**
**Description and Methods**: To derive a visual-evoked potential (VEP) technique for identifying visual field defects in children with epilepsy treated with vigabatrin and unable to perform perimetry. A field-specific VEP was developed with a central (0 degrees to 5 degrees radius) and peripheral stimulus (30 degrees to 60 degrees radius). Electroretinograms (ERG) were recorded to examine the effects of vigabatrin on retinal function. Thirty-nine children aged 3 to 15 years were included in the study. Twelve patients were examined by both the field-specific stimulus test and perimetry.
**Results**: Thirty-five of 39 children complied with the field-specific stimulus, 26 of 39 complied with the ERG, and 12 of 39 complied with perimetry. The field-specific stimulus identified 3 of 4 abnormal perimetry results and 7 of 8 normal perimetry results, giving a sensitivity of 75% and a

specificity of 87.5%. When comparing perimetry results with the ERG parameters, only the 30-Hz flicker amplitude, with a cutoff below 70 microV, gave a useful indication of visual field loss. Field-specific VEP are well tolerated by children older than 2 years of age and are sensitive and specific in identifying vigabatrin-associated peripheral field defects.

**Vanhatalo S et al. Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia 2002; 43: 748-56;**
**Description and Methods**: To study the prevalence and features of visual field constrictions (VFCs) associated with vigabatrin (VGB) in children. A systematic collection of all children with any history of VGB treatment in fifteen Finnish neuropediatric units was performed, and children were included after being able to cooperate reliably in repeated visual field tests by Goldmann kinetic perimetry. This inclusion criterion yielded 91 children (45 boys; 46 girls) between ages 5.6 and 17.9 years.
**Results**: There was a notable variation in visual field extents between successive test sessions and between different individuals. VFCs <70 degrees were found in repeated test sessions in 17 (18.7%) of 91 children. The patients with VFC had received a higher total dose of VGB. In linear regression analysis, there were statistically significant inverse correlations between the temporal extent of the visual fields and the total dose and the duration of VGB treatment. The shortest duration of VGB treatment associated with VFC was 15 months, and the lowest total dose 914 g. Although our results confirm the previous findings that VFC may occur in children treated with VGB, our study points out the need to reevaluate critically any suspected VFC to avoid misdiagnosis. Nevertheless, our study suggests that the prevalence of VFC may be lower in children than in adults, and that the cumulative dose of VGB or length of VGB therapy may add to the personal predisposition for developing VFC.

**Westall CA et al. The Hospital for Sick Children, Toronto, longitudinal ERG study of children on vigabatrin. Documenta Ophthalmologica 2002; 104: 133-49;**
**Description and Methods**: To identify changes in ERG responses associated with vigabatrin treatment by recording longitudinally ERGs in children before and during vigabatrin treatment and comparing results between children on vigabatrin monotherapy and those taking additional anticonvulsive medications.
**Results**: Thirty-three children on vigabatrin therapy were tested; the duration between visits was approximately 6 months. Thirteen children were assessed initially before starting vigabatrin therapy and seven were assessed soon after (age range 1.5-126 months, median 6 months). The remaining 13 patients were already on vigabatrin at the time of initial visit (age range 6.5-180 months, median 16 months). In addition to standard ERG responses we recorded photopic oscillatory potentials (OPs). All 33 patients were tested longitudinally on at least two occasions and 11 were tested on three occasions. For children whose only anticonvulsive drug was vigabatrin there was a significant curvature (quadratic function, $p < 0.05$) of the predicted cone b-wave amplitude with time; exhibited as increase in b-wave amplitude followed by subsequent decrease. Descriptive data demonstrated the same pattern in the group taking anticonvulsive medications in addition to vigabatrin. In most children the flicker amplitude declined between 6 months and 1 year of vigabatrin treatment. Our data demonstrated that rod responses did not change substantially with vigabatrin treatment.

**Hammoudi DS et al. Reduced visual function associated with infantile spasms in children on vigabatrin therapy. Invest Ophthalmol Vis Sci 2005; 46: 514-20;**
**Description and Methods**: To use visual evoked potential (VEP) testing to determine whether visual deficits are present in children with a history of vigabatrin use. Contrast sensitivity and visual acuity were assessed by visual evoked potential testing and compared between 28 children (mean age, 4.90 +/- 4.92 years) with seizure disorders who had taken vigabatrin and 14 typically developing children (mean age, 3.14 +/- 1.70 years). The effects of the following factors on contrast sensitivity and visual acuity were examined: type of seizure (infantile spasms versus

other), ERG result, duration of vigabatrin therapy, cumulative dosage of vigabatrin, and other seizure medications (other versus no other medication).
**Results**: Contrast sensitivity and visual acuity were reduced in vigabatrin-treated children with infantile spasms compared with vigabatrin-treated children with other seizure disorders and typically developing control subjects. Children with infantile spasms on vigabatrin may have compromised visual function, even in the absence of suspected cortical visual impairment. The children tested in the present study have reduced vision, probably associated with infantile spasms rather than vigabatrin.

**Werth R, Schadler G. Visual field loss in young children and mentally handicapped adolescents receiving vigabatrin. Invest Ophthalmol Vi Sci. 2006; 47: 3028-35;**
**Description and Methods**: The purpose of the present study was to investigate VGB-induced visual field loss in young children and mentally handicapped adolescents treated with vigabatrin by using a noncommercial arc perimeter and a forced-choice, preferential-looking method. The visual field size was measured in 30 patients aged 1 to 15 years who had epilepsy and who were treated with VGB and compared to the visual field of 70 control subjects.
**Results**: In eight (27%) patients who had been treated with VGB, the visual field was constricted compared with the visual field of the children belonging to the control group. Arc perimetry shows that mentally handicapped patients and children younger than 6 years treated with VGB have visual field loss compared with the loss reported in adult patients receiving VGB.

**You S.J. Vigabatrin and visual field defects in children with epilepsy. J Korean Med Sci 2006; 21: 728-32;**
**Description and Methods**: The aim of the study was to determine the prevalence, type and severity of vigabatrin (VGB)-attributed visual field defects (VFDs), and to assess the associated risk factors in pediatric patients. Medical records were retrospectively reviewed for 67 pediatric patients who received VGB alone or in combination with other antiepileptic drugs, and who had undergone visual field examinations using a Humphrey visual field analyzer.
**Results**: Of the 67 patients, 15 had VGB-attributed VFDs: 13 had nasal arcuate type, 1 had nasal and temporal constricted type and 1 had nasal constricted type. In terms of severity, 7 patients had Grade I VGB-attributed VFDs, 5 had Grade II, 2 had Grade III, and 1 had Grade IV. Although there were no significant differences between the VFD and non-VFD groups with regards to all tested parameters, there were no cases of VGB-attributed VFDs in patients with total treatment durations <2 yr and cumulative doses <10 g/kg. In conclusion, the prevalence of VGB-attributed VFDs in VGB-treated pediatric epilepsy patients was 22%. The high frequency of VGB-attributed VFDs indicates that physicians should inform all patients of this risk prior to VGB treatment and perform periodic visual field examinations.

**Gaily E et al. Visual fields in children treated with vigabatrin in infancy. Epilepsia 2006; 47(Suppl.4): 179-80(Abs.2176);**
**Gaily E et al. Visual fields at school-age children treated with vigabatrin in infancy. Epilepsia 2009; 50: 206-16**.
**Description and Methods**: Aim of the study was to investigate the risk of vigabatrin-attributed visual field loss (VAVFL) in school-age children who had received VGB in infancy. Visual fields of 16 children treated with VGB for infantile spasms were examined by Goldmann kinetic perimetry at age 6-12 years. Abnormal findings were always confirmed by repeating the test. Exposure data were collected from hospital charts.
**Results**: Vigabatrin was started at a mean age of 7.6 (range, 3.2-20.3) months. The mean duration of therapy was 21.0 (9.3-29.8) months and cumulative dose 655 g (209-1,109 g). Eight children were never treated with other AEDs, five received only adrenocorticotropic hormone (ACTH) in addition to VGB, and three children had been treated with other AEDs. Fifteen children had normal visual fields. Mild VAVFL was observed in one child (6%) who had been treated with VGB for 19 months and who received a cumulative dose of 572 g. The risk of

VAVFL may be lower in children who are treated with VGB in infancy compared to patients who receive VGB at a later age.

**Mirabella G et al. Contrast sensitivity is reduced in children with infantile spasms. Invest Ophthalmol Vis Sci. 2007; 48: 3610-5;**
**Description and Methods**: To investigate whether visual deficits in children with infantile spasm (IS) are the result of seizure activity or of treatment with the anticonvulsant drug vigabatrin (VGB).
**Results**: In cross-sectional study A, the median contrast sensitivity (CS) was reduced by 0.5 log units (P = 0.025) in children with epilepsy exposed to VGB compared with those exposed to other antiepileptic drugs and normally developing children. In cross-sectional study B, the median CS was reduced by 0.25 log units (P = 0.0015) in children with IS (VGB naïve) compared with normally developing children. Longitudinal assessment showed no decrease in CS in children with IS who were followed up 5 to 10 months after starting VGB. There was no difference in grating acuity (GA) among groups in any of the experiments. Patients with IS have CS deficits, but a sparing of GA. This deficit is present before VGB treatment and does not worsen with treatment onset. Results suggest that visual dysfunction is largely the result of the seizures themselves.

**Durbin S et al. Reduced grating acuity associated with retinal toxicity in children with infantile spasms on vigabatrin therapy. Invest Ophthalmol Vis Sci 2009; 50: 4011-6;**
**Description and Methods**: To determine whether visual functions are decreased in children with infantile spasms and vigabatrin-attributed retinal toxicity. Contrast sensitivity and grating acuity were measured by using sweep visual evoked potential (VEP) testing in 42 children with infantile spasms (mean age, 29.23 +/- 18.31 months). All children had been exposed to vigabatrin (VGB) for a minimum of 1 month.
**Results**: The MANOVA showed that visual function was significantly affected by VGB retinal toxicity. Further univariate analysis revealed that grating acuity was significantly reduced in children with toxicity. No differences in contrast sensitivity were found between children with toxicity and those without. Reduced visual functions from VGB-attributed retinal toxicity can be detected in children with infantile spasms with the sweep VEP.

**Wohlrab G et al. Vigabatrin therapy in infantile spasms: solving one problem and inducing another? Epilepsia 2009; 50(8): 2006-8;**
The authors conclude as follows: Our results are consistent with those in the recently published report by Gaily et al. (2009), and indicate that VFC plays a minor role in young children. We believe that the low risk of VGB-induced VFC in infancy justifies the treatment in view of the severe epileptic encephalopathy associated with infantile spasms.

*Literature references: Abnormal MRI*

**Chiron C, Dulac O et al. Magnetic resonance imaging in epileptic children treated with vigabatrin. Epilepsia 1989; 30: 736;**
The authors conclude as follows: Our results confirm the lack of abnormal findings with MRI in 16 children and infants exposed to therapeutic doses of vigabatrin for an average period of 11 months.

**Pearl PL et al. MRI Abnormalities Associated with Vigabatrin Therapy: Higher Risk in Infants? Epilepsia 2006; 47(S4): 14(Abs. PH.04);**
**Pearl PL et al. Cerebral MRI abnormalities associated with vigabatrin therapy. Epilepsia 2009; 50: 184-94.**
**Description and Methods**: To investigate whether patients on vigabatrin demonstrated new-onset and reversible T(2)-weighted magnetic resonance imaging (MRI) abnormalities. MRI of

patients treated during vigabatrin therapy was reviewed, following detection of new basal ganglia, thalamus, and corpus callosum hyperintensities in an infant treated for infantile spasms. Patients were assessed for age at time of MRI, diagnosis, duration, and dose, MRI findings pre-, on, and postvigabatrin, concomitant medications, and clinical correlation. These findings were compared to MRI in patients with infantile spasms who did not receive vigabatrin.
**Results**: Twenty-three patients were identified as having MRI during the course of vigabatrin therapy. After excluding the index case, we detected new and reversible basal ganglia, thalamic, brainstem, or dentate nucleus abnormalities in 7 of 22 (32%) patients treated with vigabatrin. All findings were reversible following discontinuation of therapy. Diffusion-weighted imaging (DWI) was positive with apparent diffusion coefficient (ADC) maps demonstrating restricted diffusion. Affected versus unaffected patients, respectively, had a median age of 11 months versus 5 years, therapy duration 3 months versus 12 months, and dosage 170 mg/kg/day versus 87 mg/kg/day. All affected patients were treated for infantile spasms; none of 56 patients with infantile spasms who were not treated with vigabatrin showed the same abnormalities. MRI abnormalities attributable to vigabatrin, characterized by new-onset and reversible T(2)-weighted hyperintensities and restricted diffusion in thalami, globus pallidus, dentate nuclei, brainstem, or corpus callosum were identified in 8 of 23 patients. Young age and relatively high dose appear to be risk factors.

**Desguerre I et al. Transient magnetic resonance diffusion abnormalities in West syndrome: the radiological expression of non-convulsive status epilepticus? Dev Med Child Neurol 2008; 50: 112-6;**
**Description and Methods**: The purpose of this study was to report patients with pharmacoresistant West syndrome of unknown cause whose magnetic resonance imaging (MRI) with diffusion weighted imaging (DWI) showed a transient decrease of diffusion in subcortical structures.
**Results**: Of 20 patients investigated over a 2-year period, three males and three females constitute the present series. They had daily clusters of infantile spasms with hypsarrhythmia for 4 to 24 months before the first investigation. Four were severely hypotonic. All aetiological studies involving intermediary metabolism, peroxysomes, mitochondria, and neurotransmitters in cerebrospinal fluid were negative. Only one responded to vigabatrin. Steroids failed in the five other patients and were followed by unsuccessful administration of various conventional medications. [All patients had vigabatrin treatment 100 mg/kg/d at first MRI.] Patients underwent DWI when first examined at the mean age of 13 months, and on follow-up examination 6 to 18 months later. Diffusion was decreased in the pallidi and posterior brainstem. It was also decreased for five patients in thalami and for three in dentate nuclei. Repeat MRI did not show the same abnormalities. Because of recruitment bias, this series probably overestimates the true incidence of such DWI abnormalities. The eventuality of toxic lesions, including some inborn error of metabolism or drug toxicity, is considered unlikely although it could not be excluded. The contribution of the epileptic encephalopathy itself appears the most likely course.

**Dracopoulos A et al. The reversible neurotoxicity of vigabatrin in infantile spasms. Epilepsia 2008; 49(Suppl 7): 86;**
Abstract. For a full paper by Dracopoulos et al., 2010, see below.

**Wheless JW et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. Epilepsia 2009; 50: 195-205;**
**Description and Methods**: A retrospective review to better characterize the frequency of MRI abnormalities in infantile spasms (IS) and in children and adults treated with vigabatrin for refractory complex partial seizures (CPS). Medical records and 332 cranial MRIs from 205 infants (aged <or=24 months) with IS treated at 10 sites in the United States and Canada were collected. Similarly, 2,074 images from 668 children (aged 2-16 years) and adults (aged >16

years) with CPS were re-reviewed. Prespecified MRI abnormalities were defined as any hyperintensity on T(2)-weighted or fluid-attenuated inversion-recovery (FLAIR) sequences with or without diffusion restriction not readily explained by a radiographically well-characterized pathology.
**Results**: Among infants with IS, the prevalence of prespecified MRI abnormalities was significantly higher among vigabatrin-treated versus vigabatrin-naive subjects (22% vs. 4%; p < 0.001). Of nine subjects in the prevalence population with at least one subsequent determinate MRI, resolution of MRI abnormalities occurred in six (66.7%)-vigabatrin was discontinued in four. Among adults and children treated with vigabatrin for CPS, there was no statistically significant difference in the incidence or prevalence of prespecified MRI abnormalities between vigabatrin-exposed and vigabatrin-naive subjects. Vigabatrin is associated with transient, asymptomatic MRI abnormalities in infants treated for IS. The majority of these MRI abnormalities resolved, even in subjects who remained on vigabatrin therapy.

**Dracopoulos A et al. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. Epilepsia. 2010;51(7):1297-304;**
**Description and Methods**: To evaluate the magnetic resonance imaging (MRI) of pediatric patients with infantile spasms (IS) treated with vigabatrin (VGB) in order to investigate whether VGB affects the brain. One hundred seven pediatric patients diagnosed with IS and treated with (n = 95) >or=120 mg/kg/day VGB or without (n = 12) VGB were included.
**Results**: Of the patients who had MRI scans during, but not before, VGB treatment (n = 81), 25 (30.9%) exhibited abnormal MRI signal intensity and/or restricted DWI in the deep gray nuclei and brainstem. Follow-up scans (performed in 15 of the 25 patients) revealed that these changes were reversible upon withdrawal of the medication. Analysis of patients undergoing scans before, during, and after VGB treatment (n = 14) revealed that four patients had abnormal MRI signal during treatment with VBG, two of whom reversed with cessation of VGB, one reversed without cessation of VGB, and another had persistent abnormal signal while being weaned from the VGB. Patients who had not received VGB treatment (n = 12) displayed normal imaging. Younger infants (<or=12 months) and those with cryptogenic IS were more likely to develop abnormal signal changes on MRI during VGB treatment. In pediatric patients, VGB induces reversible MRI signal changes and reversible diffusion restriction in the globi pallidi, thalami, brainstem, and dentate nuclei. The risk for this phenomenon was greater in younger infants and patients with cryptogenic IS.

*Literature references: Other topics*

**Vallat C et al. Treatment with vigabatrin may mimic a-aminoadipic aciduria. Epilepsia 1996; 37(8): 803-5;**
**Description and Methods**: We describe a secondary effect of treatment with vigabatrin (VGB). A significant increase in alpha-aminoadipic acid (AAA) occurred in plasma and urine of VGB-treated children, thus mimicking a known rare metabolic disease, alpha-aminoadipic aciduria (AAAuria).
**Results**: In eight out of eight children, there was a significant increase of AAA in plasma and in urine. The concentrations of AAA in these VGB-treated children were as high as the concentrations found in the inherited metabolic disease, AAAuria. This could lead to incorrect diagnosis and to inappropriate genetic counseling. Whenever a genetic metabolic disease is suspected, amino acid chromatography testing should be performed before initiation of treatment with VGB.

**Kuenzle Ch et al. Adverse effects of vigabatrin in Angelman syndrome. Epilepsia 1998; 39: 1213-5;**
**Results**: New antiepileptic drugs designed for enhancing GABAergic inhibition, such as vigabatrin (VGB) may be effective in Angelman syndrome (AS), because associated convulsions

could be related to a reduced GABA-receptor density or receptor abnormality. From our preliminary experiences in four children with AS treated with VGB, we conclude that it may induce and increase seizures in patients with AS. Vigabatrin does not seem to be appropriate in children with Angelman syndrome and epilepsy, irrespective of the type of seizures they have.

**Zelnik N et al. Vigabatrin, lamotrigine, topiramate and serum carnitine levels. Pediatr Neurol 2008; 39: 18-21;**
**Description and Methods**: To study the effect of new-generation antiepileptic drugs on serum carnitine levels. Serum carnitine levels were measured in 91 children: 24 treated with vigabatrin, 28 treated with lamotrigine, and 21 treated with topiramate. These drugs were given as monotherapy (54 children) or polytherapy (19 children). Eighteen additional children treated with valproate served as control subjects.
**Results**: Reduced mean serum carnitine level was evident only in children treated with valproate, with mean free and total carnitine level of 26.9 +/- 8.6 micromol/L and 29.1 +/- 10.4 micromol/L, respectively. In contrast, the mean serum carnitine levels of children treated with vigabatrin, lamotrigine, or topiramate were similar and normal. Only 4 children (treated with valproate) exhibited considerably lower serum carnitine levels. None of these children had significant clinical adverse effects attributable to carnitine deficiency.

In conclusion, it is well known that the overall safety profile of vigabatrin is problematic. The literature references reviewed above do not, however, provide essentially new information necessitating changes in the product information.

### 3. Discussion on clinical aspects and conclusion

The evidence for the efficacy of vigabatrin in West syndrome comes from a relatively small number of patients, but is consistent across studies and demonstrates a relatively powerful treatment effect. Most of the studies suggest that 50-60% of children treated with vigabatrin achieve complete cessation of spasms within around two weeks. The treatment effect has been demonstrated with a dose ranging from 50 to 150 mg/kg/day, but appears to be dose-related.

The response rate to vigabatrin observed in the randomised trials is replicated in the supportive studies (Aicardi et al., 1996). Concerning infantile spasms of different aetiologies, it appears that efficacy of vigabatrin is particularly high in children with tuberous sclerosis. Compared to ACTH, response to treatment with vigabatrin appears to be somewhat less rapid, but in the long-term the therapeutic efficacy of the two treatments is comparable.

In conclusion, vigabatrin is effective for the treatment of infantile spasms, particularly those related to tuberous sclerosis.

Most of the original data supporting the efficacy of vigabatrin in the treatment of refractory partial epilepsy came from fixed-sequence placebo-controlled studies, which reported treatment response rates in the range of 40% to 60%, and seizure freedom rates in the range of 15% to 20%. These response rates can be considered respectable when compared with those obtained in clinical trials of other AEDs as add-on therapy in refractory epilepsy (Cramer et al., 1999; Devinsky et al., 2000).

The only two randomised, parallel-group trials performed in paediatric patients showed comparable response rates for vigabatrin and carbamazepine. These studies were performed in newly-diagnosed patients using monotherapy treatment regimens, which do not correspond to the approved indication for vigabatrin in partial epilepsy, and where treatment response rates are expected to be higher than in studies of add-on therapy (Sander et al., 2004). A placebo-

controlled, parallel-group study using an enrichment withdrawal-randomisation design showed that vigabatrin offers acceptable seizure protection in around fifty percent of treated patients.

More information is available from clinical trials that have included both children and adults, in which overall response rates in the range of 40-60% were reported. A report of a prospective observational study of 254 patients with treatment-refractory epilepsy stated that efficacy in the 37 children (<16 years) included was comparable to efficacy in adults (Remy et al., 1989.

In conclusion, there is no new efficacy information regarding vigabatrin treatment of children with resistant partial epilepsy with or without secondary generalisation, where all other appropriate drug combinations have proved inadequate or have not been tolerated.

Pharmacokinetic studies in different paediatric age groups should be summarized taking also into account the study by Vauzelle-Kervroedan et al. (1996). Wording of the SmPC section 5.2 should be amended accordingly.

It is well known that the safety profile of vigabatrin is problematic. West's syndrome is, however, a severe condition and there is a clear medical need. Regarding partial epilepsy, there are nowadays newer, better tolerated AEDs with different mechanisms of actions available. An alternative anticonvulsant drug (or, other treatment options) can likely often be found to treat refractory patients instead using vigabatrin. Vigabatrin may, however, offer therapeutic benefit in individual paediatric cases as a "last-line agent" in clinical situations "where all other appropriate drug combinations have proved inadequate".

The product information should be amended to include the following undesirable effects: Blood and lymphatic system disorders / Anaemia (common), and Musculoskeletal and connective tissue disorders / Arthralgia (very common).

# V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

## ➢ Overall conclusion

Paediatric use of vigabatrin (Sabril®, Sabrilex®) has been evaluated in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended. Vigabatrin is currently indicated in children in the treatment of i) infantile spasms and ii) resistant partial epilepsy in combination with other anti-epileptic drugs in situations where all other appropriate drug combinations have proved inadequate or have not been tolerated. In this assessment, no essentially new efficacy information was identified but paediatric information provided in the SmPC and PL should be clarified and two new ADRs included.

## ➢ Recommendation

SmPC changes are proposed in sections 4.2, 4.6, 4.8 and 5.2 and PL changes in sections 2, 3 and 4 in order to clarify recommendations on paediatric use of vigabatrin.

Type IB variation is requested from the MAHs involved in the worksharing within 60 days after finalisation of the procedure to implement the proposal and amend the marketing authorisation as necessary.

Recommended major changes in the **SmPC** are presented below:

**4.2 Posology and method of administration**

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.

## 4.6 Fertility, pregnancy and lactation

*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).

<TRADENAME> 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 <TRADENAME> 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).

## 4.8 Undesirable effects

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 | | | | |
| ... | | | | | | |
| *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 the national reporting system listed in Appendix V.

## 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.

Recommended minor changes in the **SmPC** and **PL**:

Additional changes, such as updates according to the SmPC guideline and the latest QRD template including appendices and corresponding changes in the PL are proposed.

# VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

| Country | Local trade name | Dose form | strength | Registration holder |
|---|---|---|---|---|
| **AUSTRIA** | SABRIL 500 MG FILMTABLETTEN | film-coated tablet | 500 mg | SANOFI-AVENTIS GMBH OSTERREICH |
| **AUSTRIA** | SABRIL 500 MG LOSLICHES PULVER | granules for oral solution | 500 mg | SANOFI-AVENTIS GMBH OSTERREICH |
| **BELGIUM** | SABRIL 500 MG, COMPRIMES PELLICULES | film-coated tablet | 500 mg | SANOFI-AVENTIS BELGIUM |
| **CYPRUS** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS CYPRUS LTD |
| **CZECH REPUBLIC** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS SRO |
| **DENMARK** | SABRILEX | film-coated tablet | 500 mg | SANOFI-AVENTIS DENMARK A/S |
| **DENMARK** | SABRILEX | granules for oral solution | 500 mg | SANOFI-AVENTIS DENMARK A/S |
| **FINLAND** | SABRILEX 500 MG TABLETTI, KALVOPAALLYSTEINEN | film-coated tablet | 500 mg | SANOFI-AVENTIS OY |
| **FINLAND** | SABRILEX 500 MG JAUHE ORAALILIUOSTA VARTEN | granules for oral solution | 500 mg | SANOFI-AVENTIS OY |
| **FRANCE** | SABRIL 500 MG, COMPRIME PELLICULE | film-coated tablet | 500 mg | SANOFI-AVENTIS FRANCE |
| **FRANCE** | SABRIL 500 MG GRANULES POUR SOL. BUVABLE | granules for oral solution | 500 mg | SANOFI-AVENTIS FRANCE |
| **GERMANY** | SABRIL 500 MG FILMTABLETTEN | film-coated tablet | 500 mg | SANOFI-AVENTIS DEUTSCHLAND GMBH |
| **GERMANY** | SABRIL BEUTEL | granules for oral solution | 500 mg | SANOFI-AVENTIS DEUTSCHLAND GMBH |
| **GREECE** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS AEBE |
| **HUNGARY** | SABRIL 500 MG FILMTABLETTA | film-coated tablet | 500 mg | SANOFI-AVENTIS PRIVATE CO LTD |
| **ICELAND** | SABRILEX | film-coated tablet | 500 mg | SANOFI-AVENTIS NORGE AS |
| **IRELAND** | SABRIL 500 MG TABLETS | film-coated tablet | 500 mg | SANOFI-AVENTIS IRELAND LTD |
| **IRELAND** | SABRIL 500 MG SACHETS | granules for oral solution | 500 mg | SANOFI-AVENTIS IRELAND LTD |
| **ITALY** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS SPA |
| **ITALY** | SABRIL | granules for oral solution | 500 mg | SANOFI-AVENTIS SPA |
| **LUXEMBOURG** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS BELGIUM |
| **MALTA** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS MALTA LTD |
| **NETHERLANDS** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS NETHERLANDS B.V. |
| **NETHERLANDS** | SABRIL | granules for oral solution | 500 mg | SANOFI-AVENTIS NETHERLANDS B.V. |
| **NORWAY** | SABRILEX | film-coated tablet | 500 mg | SANOFI-AVENTIS NORGE AS |
| **NORWAY** | SABRILEX | granules for oral solution | 500 mg | SANOFI-AVENTIS NORGE AS |
| **POLAND** | SABRIL | coated tablet | 500 mg | SANOFI-AVENTIS FRANCE |
| **POLAND** | SABRIL | granules for oral solution | 500 mg | AVENTIS PHARMA LTD |
| **PORTUGAL** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS PRODUTOS FARMACEUTICOS Lda |
| **PORTUGAL** | SABRIL | granules for oral solution | 500 mg | SANOFI-AVENTIS PRODUTOS FARMACEUTICOS Lda |
| **SLOVAKIA** | SABRIL | film-coated tablet | 500 mg | SANOFI-AVENTIS SLOVAKIA SRO |
| **SLOVENIA** | SABRIL 500 MG FILMSKO OBLOZENE TABLETE | film-coated tablet | 500 mg | SANOFI-AVENTIS D.O.O. |
| **SPAIN** | SABRILEX 500 MG COMPRIMIDOS RECUBIERTOS CON PELICULA | film-coated tablet | 500 mg | MARION MERRELL S.A. |
| **SPAIN** | SABRILEX 500 MG GRANULADO PARA SOLUCION ORAL | granules for oral solution | 500 mg | MARION MERRELL S.A. |
| **SWEDEN** | SABRILEX | film-coated tablet | 500 mg | SANOFI-AVENTIS AB |
| **SWEDEN** | SABRILEX | granules for oral solution | 500 mg | SANOFI-AVENTIS AB |
| **UNITED KINGDOM** | SABRIL | film-coated tablet | 500 mg | AVENTIS PHARMA LTD |
| **UNITED KINGDOM** | SABRIL | granules for oral solution | 500 mg | AVENTIS PHARMA LTD |