



**OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
PURSUANT TO ARTICLE 12 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED, FOR**

Medicinal products

Names:	see Annex II
International non-proprietary names:	Vigabatrin
Pharmaceutical forms:	see Annex II
Strengths:	see Annex II
Route of administration:	see Annex II
Packaging and package sizes:	see Annex II

Basis for opinion

On 12 October 1998 Finland presented to the EMEA a referral under article 12 of Council Directive 75/319/EEC as amended. The grounds for referral were submitted on 12 October 1998 and are appended to this opinion. The question referred by Finland to the CPMP was:

“to give an opinion on whether there is an unfavourable benefit/risk ratio for vigabatrin, especially in relation to its potential to induce serious visual field defects.”

The referral procedure started on 21 October 1998.

The time frame agreed by the CPMP on 21 October 1998 was 180 days.

On the basis of the grounds for referral, the points considered by the CPMP were:

1. Information on vigabatrin containing medicinal product(s) available on the EU market, including information on indication(s), doses, treatment duration, sales figures and legal status.
2. Overview of the safety profile for vigabatrin containing medicinal product(s) including a specific analysis for visual disorders if any.
3. Details of all cases of visual disorders which have occurred worldwide in patients receiving vigabatrin. This should include details of diagnosis (i.e. symptomatic or asymptomatic disease), seriousness, outcome, frequency, relationship to the drug use and possible risk factors such as age, dose, duration, indication and co-medication.
4. Details of all studies which have been conducted, or those which could be conducted, to assess the incidence and prevalence of visual disorders including visual field defect, in adult and in paediatric patients who have, or have not, been treated with vigabatrin. Information about any high-risk population that could have been identified.
5. Proposals for physiopathologic explanation for these abnormalities and submit details of all studies which have been conducted to investigate the mechanism, or those which could be conducted.
6. Information available about the preventability, predictability and reversibility of visual disorders in patients receiving vigabatrin.

7. Evidence of the therapeutic benefit of vigabatrin for each approved indication, taking into account the existing therapeutic alternatives available in the EU.
8. Opinion on whether the occurrence of visual disorders in patients receiving vigabatrin modifies the benefit/risk ratio of vigabatrin containing medicinal product(s). This opinion should take into account the global safety profile and therapeutic benefit for each approved indication.
9. Specific measures which have been already taken in order to minimise the risk of visual disorders in vigabatrin receiving patients and what was their impact.
10. Proposals for any other measures which could be taken in order to improve the benefit/risk balance of vigabatrin and how their impact should be monitored and assessed.

These points were included in the list of questions sent to the Marketing Authorisation Holders referred in Annex II.

Written explanations were provided by the Marketing Authorisation Holders by 27 November 1998. Supplementary information was provided by the Marketing Authorisation Holders on 15 March 1999 and on 22 April 1999.

Oral explanations were given by the Marketing Authorisation Holders on 22 April 1999.

Opinion

The CPMP, having considered the matter as set out in the appended referral assessment report and having considered the Summary of Product Characteristics provided by the Marketing Authorisation Holders recommends the maintenance of the Marketing Authorisations of all medicinal products referred in Annex II in accordance with the Summary of Product Characteristics set out in Annex III.

The scientific conclusions and the grounds for the amendment of the Summaries of Product Characteristics are set out in Annex I.

The conditions affecting the Marketing Authorisations, as referred to in Article 13(4) of Council Directive 75/319/EEC as amended, are set out in Annex IV.

This opinion is forwarded to the European Commission, to Member States and to the Marketing Authorisation Holders, together with its annexes and appendices.

London, 20 May 1999

On behalf of the CPMP
Prof. J.-M. Alexandre, Chairman

ANNEX I
SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES
OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF VIGABATRIN CONTAINING MEDICINAL PRODUCTS

In one open follow-up study performed in Finland during the Summer of 1998 the prevalence of severe visual field constriction in patients on vigabatrin was 15% and that of any visual field constriction was 40% as compared to 0% in patients on carbamazepine or in non medicated patients. Due to these data Finland, on 12 October 1998, requested that the CPMP, under article 12 of Council Directive 75/319/EEC as amended, give an opinion on whether there is an unfavourable benefit/risk ratio for vigabatrin, especially in relation to its potential to induce serious visual field defects.

The CPMP at their meeting of 18-20 May 1999 considered the matter and reached the following conclusions, based on the joint Assessment Report prepared by the Rapporteur and the Co-Rapporteur.

SAFETY

The overall safety profile of vigabatrin was reviewed. The main safety concern discussed was visual field defects (VFD).

Visual Field Defects

Preclinical data related to ocular toxicity

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

Preclinical pharmacokinetic studies in rats provide evidence of melanin binding of vigabatrin. Melanin binding may actually be a protective factor in pigmented animals as the local free concentration of the drug may be decreased.

Visual Field Defects in adults

The Marketing Authorisation Holders (MAHs) have received altogether 363 reports of visual field defects by November 15, 1998. Of a total of 208 visual field charts obtained by the MAHs, 87 represented a typical visual field defect consisting of a binasal concentric constriction defect with relative sparing of the temporal field. According to the available data, the cases of visual field loss appear to be mostly non-symptomatic and, hence, the true prevalence in vigabatrin users is probably much higher than what is suggested by spontaneous reports.

An updated estimation of the prevalence, cumulative incidence, severity and risk factors of vigabatrin associated VFD was analysed. For the update, cohorts of vigabatrin patients from open-label extensions of 7 clinical studies were used.

From the pooled patient cohort 335 vigabatrin patients above 14 years of age had usable visual field results. Of these, 31% (95% CI 26%-37%) manifested a vigabatrin attributed VFD as compared to 0% (upper 95% CI 3%) in the unexposed control cohort.

Concerning cumulative incidence of VFD as a function of duration of vigabatrin therapy, the cumulative incidence of cases of VFD increased rapidly in the first two years of treatment, then slightly stabilised at 3 years. However, the number of patients with treatment duration exceeding 5-6

years was small. There is no reliable evidence that the risk of developing vigabatrin attributed VFD decreases after the initial three years of treatment.

The association between the cumulative incidence of VFD as a function of cumulative vigabatrin dose was investigated in a cohort of 291 patients. The prevalence of VFD in this cohort was 30.2%. A steep increase in the cumulative incidence within the first two kilograms of vigabatrin intake was found. The incidence appeared to plateau after a total of 3 kg of vigabatrin intake (i.e. 3 g/day for approximately one year).

The severity of vigabatrin attributed VFD could be determined for 92 patients. Of these, 22% were Grade 1, 31% Grade 2, 27% Grade 3 and 20% Grade 4. The overall rate of symptoms was 4.4%, 6% of those with Grade 3 VFD and 12.5% of those with Grade 4 VFD. The mean severity grade of VFD was similar for all strata of treatment duration.

Concerning risk factors an association was found for male gender and the occurrence of vigabatrin attributed visual field loss with a crude relative risk (cumulative incidence ratio) of 1.9 (CI 1.4-2.7). No association was found for age, weight, body mass index and duration of epilepsy.

The true incidence, progression rate and the proportion of visual field defects progressing from mild to severe are currently unknown. Limited published reports suggest that the visual field defects are irreversible even after discontinuation of vigabatrin treatment. Because most of the cases are asymptomatic, they can only be identified by performing routine visual field assessment using a standardised approach.

Visual Field Defects in children

Only 22 children below the age of 14 years enrolled in clinical studies had yielded reliable perimetry results and two cases of vigabatrin attributed VFD were identified. The cumulative incidence was 9.1% (95% CI 1%-29%). Due to the limited data no further analysis could be undertaken and a difference in the risk of VFD in children as compared to adults cannot be concluded.

No reliable information of the prevalence of VFD attributable to vigabatrin exists in children. Hence, the small number of ADR reports in children must currently be attributed to the difficulties in the diagnosis of visual field abnormalities.

Assessment of visual fields in children less than 9 years of developmental age is seldom possible. Other methods, such as electroretinogram and field-specific visual evoked potentials have not been validated in the diagnosis/exclusion of vigabatrin attributed VFD.

There is no information on the possible occurrence of VFD in children who have been exposed to vigabatrin *in utero*.

EFFICACY

Treatment of partial epilepsy in adults

In randomised placebo-controlled crossover and parallel group studies in patients with therapy resistant partial epilepsy, add-on vigabatrin treatment has resulted in at least 50% reduction in seizure frequency in approximately 40% of patients. However, in controlled trials with other antiepileptic drugs, vigabatrin monotherapy has been slightly less effective than carbamazepine monotherapy. The daily dose of vigabatrin has generally been 2-3 g and according to a large randomised study, higher doses are not associated with increased efficacy. There are no data on direct comparisons of vigabatrin with other antiepileptic drugs as add-on treatment. Vigabatrin may increase the frequency of absence and myoclonic seizures.

Treatment of partial epilepsy in children

Epilepsy in children differs to a large extent from epilepsy in adults and should be considered

separately with regard to incidence, epileptic seizures and syndromes, consequences of childhood refractory epilepsy on psychomotor development and social integration.

Like in adults, 20-30% of children with epilepsy do not obtain control of seizures with conventional anticonvulsant medication, justifying that the need for more effective anticonvulsant medication is as least as great as in adults (*Pellock 1989; Dodson 1993; Heller 1993*).

In children with therapy resistant partial epilepsy, greater than 50% reduction in seizure frequency has been observed in 40-60% of patients during add-on vigabatrin treatment. Vigabatrin has been effective in both simple and complex partial seizures and in the control of secondary generalization. Long-term follow up studies of children with therapy resistant epilepsy have generally demonstrated adequate control of partial epilepsies with or without secondary generalization. However, in the Lennox Gastaut syndrome, neither short-term nor long-term results are encouraging and an increase in myoclonic seizures has even been observed.

No controlled studies are available to assess the efficacy of vigabatrin monotherapy in children. No comparative trials are available to assess the efficacy of vigabatrin compared to other anticonvulsants, including newer drugs, such as oxcarbazepin, felbamate, lamotrigine and topiramate which are approved in some EU Member States for childhood epilepsy in children over 2-4 years of age.

Treatment of Infantile Spasms (West's syndrome)

Vigabatrin has been found to be an effective treatment for infants with infantile spasms. In controlled trials, vigabatrin monotherapy produced higher clinical response rates than placebo or oral hydrocortisone. Vigabatrin monotherapy appears to be less effective than ACTH, but is generally better tolerated than ACTH treatment which is associated with severe undesirable effects

RISK-BENEFIT ANALYSIS

Risk-benefit in adults

The risk-benefit profile of vigabatrin as monotherapy in adult patients with epilepsy is negative due to safety concerns (severe psychiatric reactions and risk of visual field defect) and due to inferior efficacy compared to carbamazepine.

The risk-benefit profile of vigabatrin as an add-on treatment in adult patients with therapy resistant partial epilepsy with or without secondary generalization in cases where all other appropriate drug combinations have proved inadequate or have not been tolerated may only be considered positive if the Summaries of Product Characteristics are amended as required and the MAHs commit themselves to fulfil the requirements of the CPMP with regard to preclinical and clinical studies and follow-up measures.

Risk-benefit in children

The risk-benefit profile of vigabatrin monotherapy in children with partial epilepsy is negative.

The risk-benefit profile of vigabatrin as an add-on treatment in pediatric patients with therapy resistant partial epilepsy with or without secondary generalization in cases where all other appropriate drug combinations have proved inadequate or have not been tolerated may only be considered positive if the Summaries of Product Characteristics are amended as required and the MAHs commit themselves to fulfil the requirements of the CPMP with regard to preclinical and clinical studies and follow-up measures.

With the same reservations, the risk-benefit profile of vigabatrin monotherapy in children with infantile spasms is considered positive. The treatment alternatives (ACTH, corticosteroids) in this indication are associated with severe and life-threatening undesirable effects.

Therefore the CPMP considered that the risk-benefit balance of vigabatrin containing medicinal

products is favourable and the Marketing Authorisations should be maintained provided that:

- The Summaries of Product Characteristics are amended as stated in Annex III with emphasis to the following:
 - Restriction of the indications to 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 and to monotherapy in the treatment of infantile spasms (West's syndrome).

 - Initiation of the treatment by a specialist in epileptology, neurology or paediatric neurology and follow-up should be arranged under supervision of a specialist in epileptology, neurology or paediatric neurology.

 - Inclusion of warnings in relation to the occurrence of VFD and the need for systematic screening examination of patients when starting vigabatrin and at regular intervals for detection of VFD.

 - Update of the section of Undesirable Effects including a wording on VFD and their severity, onset and prevalence.

- The MAHs should fulfil the CPMP requirements set out in Annex IV with regard to:
 - Preclinical studies
Preclinical studies should be performed to investigate the mechanisms of vigabatrin induced retinotoxicity and to provide information regarding the possible differences in sensitivity to retinotoxicity in young and adult animals.

 - Clinical studies
Clinical studies to evaluate the frequency, severity, progression and reversibility of VFD should be performed.

 - Patient follow-up
Patient follow-up should include data on the prevalence and characteristics of VFD in children who have been exposed to vigabatrin and 6 months reviews of follow-up data from marketed use and spontaneous reports.

GROUNDS FOR THE AMENDMENT OF THE SUMMARIES OF PRODUCTS CHARACTERISTICS

Whereas

- the Committee considered the referral made under article 12 of Council Directive 75/319/EEC as amended for vigabatrin containing medicinal products

- the Committee agreed that there was particular concern related to the safety of vigabatrin containing medicinal products in relation to the risk of visual field defects and therefore the safety profile of vigabatrin containing medicinal products is only acceptable if it is used according to strict conditions

- the Committee agreed that vigabatrin containing medicinal products are effective as an add-on treatment in adult and children patients with therapy resistant partial epilepsy with or without secondary generalization and as monotherapy in children with infantile spasms

- the Committee considered the risk/benefit balance of vigabatrin containing medicinal products to be favourable as an add-on treatment in adult and children patients with therapy resistant partial

epilepsy with or without secondary generalization in cases where all other appropriate drug combinations have proved inadequate or have not been tolerated, and in monotherapy in children with infantile spasms, and, therefore, concluded that the Marketing Authorisations for these medicinal products should be maintained if amended in accordance with the Summary of Product Characteristics as set out in Annex III and under the conditions set out in Annex IV,

the CPMP has recommended the maintenance of the Marketing Authorisations for vigabatrin containing medicinal products (see Annex II) in accordance with the SPC set out in Annex III and under the conditions set out in Annex IV.

ANNEX II
LIST OF THE NAMES OF THE MEDICINAL PRODUCTS, MARKETING
AUTHORISATION HOLDERS, PHARMACEUTICAL FORMS, STRENGTHS, ROUTE OF
ADMINISTRATION, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

VIGABATRIN CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE EU

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Austria	Hoechst Marion Roussel GmbH Altmannsdorferstr. 104 A-1121 Wien	Sabril 500 mg - Filmtabletten	film coated tablet	500 mg	Oral	blister 100
Austria	Hoechst Marion Roussel GmbH Altmannsdorferstr. 104 A-1121 Wien	Sabril 500 mg - Lösliches Pulver	powder for oral solution	500 mg	Oral	sachet 50
Austria	Hoechst Marion Roussel GmbH Altmannsdorferstr. 104 A-1121 Wien	Sabril 1g - Lösliches Pulver	powder for oral solution	1g	Oral	sachet 50
Belgium	Hoechst Marion Roussel 155, rue Colonel Bourg B-1140 Brussels	Sabril	tablet	500 mg	Oral	blister 50 100
Denmark	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	tablet	500 mg	Oral	blister 100
Denmark	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	powder for oral solution	500 mg	Oral	sachet 50
Denmark	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	powder for oral solution	1g	Oral	Not yet marketed
Denmark	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	powder for oral solution	2g	Oral	Not yet marketed

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Denmark	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	powder for oral solution	3 g	Oral	Not yet marketed
Finland	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	powder	500 mg	Oral	sachet 50
Finland	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	film coated tablet	500 mg	Oral	blister 100
France	Marion Merrel S.A. 1, Terrasse Bellini 92800 Puteaux	Sabril comprimés	tablet	500 mg	Oral	blister 60
France	Marion Merrel S.A. 1, Terrasse Bellini 92800 Puteaux	Sabril poudre pour solution orale	powder for oral solution	500 mg	Oral	sachet 60
Germany	Hoechst AG Brüningstr. 50 D-65929 Frankfurt	Sabril Sachets 1g	granules	1g	Oral	sachet 50 100
Germany	Hoechst AG Brüningstr. 50 D-65929 Frankfurt	Sabril Sachets 2g	powder for oral solution	2g	Oral	sachet 50 100
Germany	Hoechst AG Brüningstr. 50 D-65929 Frankfurt	Sabril Sachets 3g	powder for oral solution	3g	Oral	sachet 50 100
Germany	Hoechst AG Brüningstr. 50 D-65929 Frankfurt	Sabril Beutel	granules	500 mg	Oral	sachet 50 100

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Germany	Hoechst AG Brüningstr. 50 D-65929 Frankfurt	Sabril Filmtabletten	film coated tablet	500 mg	Oral	blister 50 100 200 500
Germany	Hoechst AG Brüningstr. 50 D-65929 Frankfurt	Sabril Tabletten	tablet	500 mg	Oral	blister 50 100 200 500
Greece	Hoechst Marion Roussel Kifissias Avenue 32 Atrina 15110 Marousi	Sabril	powder for oral solution	500 mg	Oral	sachet 50
Greece	Hoechst Marion Roussel Kifissias Avenue 32 Atrina 15110 Marousi	Sabril	powder for oral solution	1 g	Oral	sachet 50
Greece	Hoechst Marion Roussel Kifissias Avenue 32 Atrina 15110 Marousi	Sabril	powder for oral solution	2 g	Oral	sachet 50
Greece	Hoechst Marion Roussel Kifissias Avenue 32 Atrina 15110 Marousi	Sabril	powder for oral solution	3 g	Oral	sachet 50
Greece	Hoechst Marion Roussel Kifissias Avenue 32 Atrina 15110 Marousi	Sabril	film coated tablet	500 mg	Oral	blister 20 30

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Ireland	Marion Merrell Ltd Broadwater Park Denham Uxbridge Middlesex UB9 5HP	Sabril	tablet	500 mg	Oral	blister 100
Ireland	Marion Merrell Ltd Broadwater Park Denham Uxbridge Middlesex UB9 5HP	Sabril	powder for oral solution	500 mg	Oral	sachet 50
Italy	Hoechst Pharma S.p.A Via R. Lepetit, 8 20020 Lainate (MI)	Sabril	tablet	500 mg	Oral	blister 50
Italy	Hoechst Pharma S.p.A Via R. Lepetit, 8 20020 Lainate (MI)	Sabril	powder	500 mg	Oral	sachet 50
Italy	Hoechst Pharma S.p.A Via R. Lepetit, 8 20020 Lainate (MI)	Sabril	Powder	1 g	Oral	sachet 24
Luxembourg	Hoechst Marion Roussel 155, rue Colonel Bourg B-1140 Brussels Belgium	Sabril	tablet	500 mg	Oral	blister 50 100
Luxembourg	Hoechst Marion Roussel 155, rue Colonel Bourg B-1140 Brussels Belgium	Sabril	powder	500 mg	Oral	sachet 50
Luxembourg	Hoechst Marion Roussel 155, rue Colonel Bourg B-1140 Brussels Belgium	Sabril	powder	1 g	oral	sachet 50

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Luxembourg	Hoechst Marion Roussel 155, rue Colonel Bourg B-1140 Brussels Belgium	Sabril	powder	2 g	oral	sachet 50
Netherlands	Yamanouchi Pharma B.V. Postbus 108 2350 AC Leiderdorp	Sabril, tabletten 500 mg	coated tablet	500 mg	oral	blister 100 plastic bottle 1000
Netherlands	Yamanouchi Pharma B.V. Postbus 108 2350 AC Leiderdorp	Sabril, poeder in sachets 0,5 gram	powder	500 mg	oral	sachet 50
Netherlands	Yamanouchi Pharma B.V. Postbus 108 2350 AC Leiderdorp	Sabril, poeder in sachets 1 gram	powder	1 g	oral	sachet 50
Netherlands	Yamanouchi Pharma B.V. Postbus 108 2350 AC Leiderdorp	Sabril, poeder in sachets 2 gram	powder	2 g	oral	sachet 50
Netherlands	Yamanouchi Pharma B.V. Postbus 108 2350 AC Leiderdorp	Sabril, poeder in sachets 3 gram	powder	3 g	oral	sachet 50
Portugal	Marion Merrell Lda Estrada Nacional 249, Km 15 2725 Mem Martins	Sabril	coated tablet	500 mg	oral	blister 20 60
Portugal	Marion Merrell Lda Estrada Nacional 249, Km 15 2725 Mem Martins	Sabril	powder for oral solution	500 mg	oral	sachet 20

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Portugal	Marion Merrell Lda Estrada Nacional 249, Km 15 2725 Mem Martins	Sabril	powder for oral solution	1 g	oral	sachet 20
Portugal	Marion Merrell Lda Estrada Nacional 249, Km 15 2725 Mem Martins	Sabril	powder for oral solution	2 g	oral	sachet 20
Portugal	Marion Merrell Lda Estrada Nacional 249, Km 15 2725 Mem Martins	Sabril	powder for oral solution	3 g	oral	sachet 20
Spain	Marion Merrell SA Ronda General Mitre 72-74 08017 Barcelona	Sabrillex	tablet	500 mg	oral	blister 100
Spain	Marion Merrell SA Ronda General Mitre 72-74 08017 Barcelona	Sabrillex	powder for oral solution	500 mg	oral	sachet 50
Sweden	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	tablet	500 mg	oral	blister 100
Sweden	Hoechst Marion Roussel AB Bryggvägen 16-18 11768 Stockholm Sweden	Sabrillex	powder	500 mg	oral	sachet 50
UK	Marion Merrell Ltd Broadwater Park Denham, Uxbridge Middlesex UB9 5HP	Sabril Sachets	powder	500 mg	oral	sachet 50
UK	Marion Merrell Ltd Broadwater Park Denham, Uxbridge Middlesex UB9 5HP	Sabril Tablets	tablet	500 mg	oral	blister 100

ANNEX III
SUMMARY OF PRODUCT CHARACTERISTICS

1 TRADE NAME OF THE MEDICINAL PRODUCT

<TRADENAME>

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains:

Vigabatrin 500 mg /1 g/2 g/3 g

Each tablet/coated tablet/film coated tablet contains:

Vigabatrin 500 mg

3 PHARMACEUTICAL FORM

Oral powder/Granules/Tablet/Coated tablet/Film coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary 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).

4.2 Posology and method of administration

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

<TRADENAME> is for oral administration once or twice daily and may be taken before or after meals. Sachet contents may be placed in beverage (e.g. water, fruit juice or milk) immediately before oral administration.

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

Adults

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

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

Children

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

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

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

Infants - 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.

Elderly and Patients with Renal Impairment

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

4.3 Contraindications

Hypersensitivity to vigabatrin or to any excipient in the medicinal product.

4.4 Special warnings and special precautions for use

Except for the treatment of infantile spasms, <TRADENAME> should not be initiated as monotherapy.

Visual field defects have been reported in patients receiving vigabatrin with a high prevalence (about 1/3 of patients). The onset is usually after months to years of vigabatrin therapy. The degree of visual field restriction may be severe and this may have practical consequences for the patient. Most of the patients with perimetry-confirmed defects have been asymptomatic. Hence, this undesirable effect can only be reliably detected by systematic perimetry which is usually possible only in patients with a developmental age of more than 9 years.

A specifically developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test the presence of peripheral vision in children aged 3 years and above. At present this method has not been validated in the detection of vigabatrin attributed visual field defects. Electroretinography may be useful but should be used only in adults who are unable to cooperate with perimetry or in the very young (see Visual Field Defects).

Available data suggests that visual field defects are irreversible even after discontinuation of vigabatrin.

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

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

Patients should undergo systematic screening examination when starting vigabatrin and at regular intervals for detection of visual field defects (see Visual Field Defects).

Visual Field Defects (VFD)

Based on available data, the usual pattern is a concentric constriction of the visual field of both eyes, which is generally more marked nasally than temporally. In the central visual field (within 30 degree of eccentricity), frequently an annular nasal defect is seen. Central visual acuity is not impaired. However, the VFDs reported in patients receiving vigabatrin have ranged from mild to severe. Severe cases are potentially disabling.

Most patients with perimetry-confirmed defects had not previously spontaneously noticed any symptoms, even in cases where a severe defect was observed in perimetry. Available evidence suggests that the VFD is irreversible even after discontinuation of vigabatrin.

Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy have VFDs. Males may be at greater risk than females.

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

If possible, appropriate visual field testing (perimetry) by using a standardized static perimetry (Humphrey or Octopus) or kinetic perimetry (Goldmann) must be performed before treatment initiation and at six month intervals. Static perimetry is the preferred method for detecting vigabatrin associated visual field defect.

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

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

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

Vigabatrin should not be used concomitantly with other retinotoxic drugs.

Children

Perimetry is seldom possible in children less than 9 years of developmental age. The risks of treatment must be very carefully weighed against possible benefit in children. Currently, there is no established method to diagnose or exclude visual field defects in children in whom a standardized perimetry cannot be performed. A specifically developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test the presence of peripheral vision in children aged 3 years and above. At present this method has not been validated in the

detection of vigabatrin attributed visual field defects. If the method reveals normal central visual field response but an absent peripheral response, benefit-risk of vigabatrin must be reviewed and consideration given to gradual discontinuation. The presence of peripheral vision does not exclude the possibility of a developing VFD. Electroretinography may be useful but should be used only in children less than 3 years of age.

Neurological and psychiatric conditions

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

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

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

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

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

Elderly and patients with renal impairment

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

in patients taking vigabatrin. (See Section 4.8 Undesirable effects).

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

4.6 Pregnancy and lactation

Data on a limited number (n=192) of exposed pregnancies are available. Congenital anomalies were reported in 14.5% of exposed pregnancies. Of these, 64.3% were major malformations. Spontaneous abortion was reported in 10.9% of exposed pregnancies. No definite conclusion can be drawn as to whether vigabatrin produces an increased risk of malformation when taken during pregnancy because of limited data, epilepsy itself, and the presence of concomitant antiepilepsy medicinal products during each reported pregnancy.

There is no information on the possible occurrence of visual field defect in children who have been exposed to vigabatrin *in utero*.

Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). The relevance of these data for humans is unknown.

If a patient becomes or wishes to become pregnant, treatment should be reviewed. Sudden interruption of effective antiepileptic treatment may lead to aggravation of the condition in the mother that is detrimental to the foetus.

Vigabatrin should only be used during pregnancy if clearly necessary.

Vigabatrin is excreted into breast milk. Breastfeeding is not recommended during vigabatrin treatment.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

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

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

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency, including status epilepticus with vigabatrin. Patients with myoclonic seizures may be particularly

liable to this effect. New onset myoclonus and exacerbation of existing myoclonus may occur in rare cases.

Very common (>1/10)	<i>General disorders:</i> <i>Psychiatric disorders</i> *: <i>Eye disorders:</i>	Somnolence, fatigue Excitation and agitation (children) Visual field defect
Common (>1/100, <1/10)	<i>General disorders:</i> <i>Nervous system disorders:</i> <i>Psychiatric disorders</i> *: <i>Gastrointestinal disorders:</i> <i>Eye disorders:</i>	Headache, weight gain, tremor, oedema Dizziness, paresthesia, disturbance of concentration and memory Agitation, aggression, nervousness, irritability, depression, thought disturbance, paranoid reaction Nausea, abdominal pain Blurred vision, diplopia, nystagmus
Uncommon (>1/1,000, <1/100)	<i>Nervous system disorders:</i> <i>Psychiatric disorders</i> *: <i>Skin disorders:</i>	Ataxia Hypomania, mania, psychosis Rash
Rare (<1/1,000)	<i>General disorders:</i> <i>Nervous system disorders:</i> <i>Psychiatric disorders:</i> <i>Eye disorders:</i>	Angioedema, urticaria Encephalopathic symptoms** Suicide attempt Retinal disorder (such as peripheral retinal atrophy)
Very rare (<1/10,000)	<i>Eye disorders:</i>	Optic neuritis, optic atrophy

*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 Special warnings and special precautions for use). 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 Special warnings and special precautions for use).

Laboratory data indicate that vigabatrin treatment does not lead to renal or hepatic toxicity. Decreases in ALT and AST, which are considered to be a result of inhibition of these aminotransferases by vigabatrin, have been observed. Chronic treatment with vigabatrin may be associated with a slight decrease in haemoglobin which rarely attains clinical significance.

4.9 Overdose

Symptoms

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

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group : Antiepileptics, ATC code: N03AG04

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

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

5.2 Pharmacokinetic properties

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

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

Vigabatrin is eliminated from the plasma with a terminal half-life of 5-8 hours with approximately 70% of a single oral dose being recovered as unchanged drug in the urine in the first 24 hours post-dose. No metabolites have been identified.

Vigabatrin does not induce the hepatic cytochrome P450 enzymes nor is it metabolised or protein bound. Therefore drug interactions are unlikely.

5.3 Preclinical safety data

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

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

study indicate that intramyelinic oedema is associated with an increase in the latency of the somatosensory evoked potential which is reversible when the drug is withdrawn.

In humans, there is no evidence of intramyelinic oedema. Tests done to confirm lack of significant adverse effect on neurological function include evoked potentials, CAT scans, magnetic resonance imaging, CSF analyses and in a small number of cases, neuropathological examinations of brain specimens.

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

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

Studies with vigabatrin revealed no evidence of mutagenic or carcinogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

6.3 Shelf-life

6.4 Special precautions for storage

6.5 Nature and contents of container

6.6 Instructions for use and handling

7 MARKETING AUTHORISATION HOLDER

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10 DATE OF (PARTIAL) REVISION OF THE TEXT

ANNEX IV
CONDITIONS OF THE MARKETING AUTHORISATIONS

Conditions of the Marketing Authorisations
CPMP requirements in relation to preclinical studies, clinical studies
and patient follow-up

Preclinical studies

The mechanisms of vigabatrin-induced retinotoxicity need further clarification through a series of preclinical studies focusing on:

- 1) Investigation of possible phototoxic component in pigmented and non-pigmented rats;
- 2) Study of the effects of vigabatrin on the retina, retinal and vitreous humor GABA, glutamate and glutamine concentrations.

Preclinical studies could provide some information regarding the possible differences in sensitivity to retinotoxicity in young and adult animals. Therefore, the above-mentioned studies must be performed in both young and adult animals. Furthermore, toxicokinetic studies using repeated dosing must be performed to characterise the disposition of vigabatrin specifically in ocular tissues.

A time-schedule for these studies should be provided and the results must be submitted to the CPMP for review as soon as they become available, but within 12 months from the CPMP opinion. 6-monthly updates on the progress of all preclinical studies should be provided.

Clinical studies

Future studies to evaluate the frequency, severity and progression of visual field defects must be performed. In these clinical studies visual field examination under standardised, repeatable and comparable conditions (Goldmann kinetic perimetry, or Humphrey or Octopus static perimetry) should be performed. If possible multifocal electroretinography (performed according to ISCEV standards) should also be carried out. Centers able to perform both tests should be favoured.

Baseline investigations must be performed to enable monitoring of changes in visual fields and multifocal ERG during vigabatrin treatment. Comparative studies in patients receiving other antiepileptic drugs should also be performed. In patients who are receiving vigabatrin, electrophysiological measures should be performed regardless of the presence of any visual field defect. Specific physiopathologic abnormalities associated with visual field defect can only be identified through these studies and studies in patients who are withdrawn from vigabatrin treatment.

In all studies, the inclusion criteria should be in line with the required restricted indications (i.e. second line add-on treatment).

The study protocols must be submitted for review within 3 months from the CPMP opinion and 6-monthly updates on the progress of all current and future clinical studies should be provided.

Patient follow-up

All available and recoverable information on the prevalence and characteristics of visual field defect in children who have been exposed to vigabatrin during first years of life (especially children with infantile spasms), in children who have been treated later during childhood, and in children who have been exposed *in utero*, and in whom reliable visual field examination can be performed, should be provided on an ongoing basis. The MAHs should provide a plan to clarify the strategy to fulfil this commitment.

6-monthly reviews of follow-up data from marketed use and spontaneous reports must be provided.