ビガバトリン

1．医薬品名、剤型、必要と考えられる対象年齢、効能・効果（対象疾患）、対象患者数	
a．医薬品名（一般名・商標名）	一般名：(和)ビガバトリン、(洋)Vigabatrin、商品名：Sabril®
b．剤型	錠剤、細粒剤
c．現在市販されている剤型で対応可能か	(はい)・いいえ
d．対象年齢	3ヵ月～5歳
e．効能・効果、対象疾患	点頭てんかん（Infantile spasms） 成人と同一か否か：はい・いいえ（　　） 他にも適応となる効能・効果、対象疾患があるか：はい・ (いいえ)（はいの場合は以下に記載）
f．年間症例数の予測 （5万例を超えるか？）	出生10,000人に対し3.1人。 （平成14年度出生数：115万人 → 356人）
2．国内外での開発・販売企業と開発状況	
a．国内での開発・販売企業	アベンティス ファーマ株式会社
b．国内での成人および小児の開発状況	成人での承認　有／無　承認年月日（　　） 小児での承認　有／無（　　） 開発状況（製剤追加の場合も含む） 開発中断。
c．海外での開発・販売企業	Aventis Pharmaceuticals Inc.
d．海外での成人および小児の開発・承認状況	成人での承認　有／(無)　承認年月日イギリス（1989）など 小児での承認　有／(無) 開発中であれば開発国と開発状況を記載
3．日本の添付文書の記載内容　：　該当せず	
a．商標名	
b．効能・効果、対象疾患	
c．用法・用量	
d．使用上の注意、慎重投与、禁忌等の記載内容	
e．その他の問題点	
f．現在の記載でどういう現実的な問題があるのか	
4．海外の添付文書の記載内容、承認状況（できれば数ヶ国について）	
米国の状況　：　該当せず	承認状況： 添付文書の記載内容： 効能・効果、対象疾患 用法・用量 使用上の注意、慎重投与、禁忌等の記載内容
海外の状況	承認状況： イギリス（1989）、フランス（1991）、ドイツ（1992）、イタリア（1992）等60カ国以上

	添付文書の記載内容： 【効能・効果、対象疾患】 ・他の抗てんかん薬治療において発作のコントロールが十分でない治療抵抗性の部分てんかん患者に対する他の抗てんかん薬との併用療法 ・点頭てんかん（West 症候群）治療における単剤療法 【用法・用量】 ・成人：最大効果は 2～3g/日の範囲で認められる。開始用量は 1 日 1g、症状等に応じて週 1 回の間隔で 0.5g ずつ増量。最高推奨用量は 3g/日。 ・小児：推奨開始用量は 40mg/kg/日。各体重における推奨維持用量は以下のとおりである。 10～15kg　0.5～1.0g/日 15～30kg　1.0～1.5g/日 30～50kg　1.5～3.0g/日 50kg＜　2.0～3.0g/日 点頭てんかん（West 症候群）に対する単剤療法における推奨開始用量は 50mg/kg/日。必要に応じて 1 週間かけて増量しても良い。150mg/kg/日までの耐性は良好。 【使用上の注意、慎重投与、禁忌等の記載内容】 ・投与患者の約 1/3 に視野狭窄が報告されている。そのためリスク/ベネフィットを考慮し慎重に使用を決定する。また、投与においては、定期的な視野検査を実施すること。 ・他の副作用としては、眠気、めまい、易刺激性、倦怠感、頭痛、ふらつき、吐気、便秘、幻覚妄想、興奮、不眠、GOT・GPT の低下等が報告されている。 ・一般的注意注意：①眠気等が起こることがあるので、本剤投与中の患者には自動車運転等危険な機械の操作には従事させないよう注意する。②精神病や進行性の神経疾患を合併している患者、てんかん重積状態または薬物過敏症の患者、妊婦・授乳婦には投与しない。③投与を終了・中止する時は原則として徐々に減量する。
5．エビデンスのレベル（別に添付資料としても可、レファレンスはコピーを必ず保存）	
Cochran Review の評価 （全文は資料として別添）	Treatment of infantile spasms (Cochrane Review), Hancock E, Osborne JP, Milner P –ABSTRACT – **Main results:** Ten small RCTs were included. In total these studies recruited just 335 participants and tested eight different drugs. Overall, studies were of poor methodological quality. No study assessed long-term psychomotor development or the development of other seizure types. One small study found vigabatrin to be more efficacious than hydrocortisone in stopping infantile spasms in a group of people with tuberous sclerosis. One underpowered study showed a trend for vigabatrin to be more efficacious than placebo in stopping infantile spasms, two small studies when combined showed ACTH to be more efficacious than low-dose prednisone (2mg/kg). It was not possible to compare reduction in the number of spasms between the different treatments because of differences in methods of analysis. Overall, only nine participants were reported to have been withdrawn from the trial treatments due to side effects and two deaths were reported. **Reviewers' conclusions:** We found no reliable evidence that any of the treatments assessed were more efficacious than any other. Few studies considered psychomotor development or subsequent seizure rates as outcomes and none had long term follow-up. Further trials with larger numbers of participants, and longer follow-up are required.
Cochran Review の採用文献	（別添可）
5－1．国内外の代表的な教科書、一流雑誌の総説、ガイドラインにおける記載	
教科書（雑誌）名、ページ、版、発行年など	記載内容のサマリー

Report of the ILAE Task Force on Classification and Terminology (Date of update: December 12, 1998) http://www.epilepsy.org/ctf/syn_frame.html West syndrome by Oliver Dulac Date of submission: November 19, 1993 Date of update: December 12, 1998 Medline SEARCH DATE: December 1998	**Management** Previously, among antiepileptic drugs only valproic acid and nitrazepam were reported to be effective in treating patients with infantile spasms. Dreifuss has suggested that nitrazepam and adrenocorticotropic hormone afford a similar degree of seizure control, although there is no general agreement (Dreifuss et al 1986). Recently, vigabatrin (gamma vinyl GABA), an antiepileptic medication available in Canada, Europe, South America, India, and the Middle East, has been used with success in the treatment of infantile spasms, as confirmed in a double-blind study against placebo (Appleton and Montiel-Viesca 1993). A randomized study has shown better effect of vigabatrin than steroids in infantile spasms due to tuberous sclerosis (Chiron et al 1997).
Infantile spasms (West Syndrome) information sheet compiled by the National Institute of Neurological Disorders and Stroke (NINDS). NINDS Infantile Spasms Information Page Synonym(s): WestSyndrome ,Reviewed 07-01-2001 .http://www.ninds.nih.gov/health_and_medical/ disorders/ infantilespasms.htm	**Is there any treatment?** Some patients may be treated successfully with either ACTH (adrenocorticotrophic hormone) or prednisone. Newer antiepileptic medications, such as vigabatrin, and occasionally surgical resection of a seizure focus which triggers the spasms, may be useful in selected patients.
Dulac O, Tuxhorn I. Chapter 4 Infantile spasms and West syndrome. In:Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, editors. Epileptic Syndromes in Infancy, Childhood and Adrescence. 3rd ed. London: John Libbey & Co Ltd, 2002. p.47-63.	**Drug treatment** The major drugs that have been shown to be effective in IS are steroids and Vigabatrin. In addition, some patients respond to valproic acid, lamotrigine, high doses of pyridoxine, topiramate and zonisamide. Most conventional anti-epileptic compounds are ineffective. Carbamazepine may even worsen the condition – an important finding in view of the possible combination of IS with focal seizures. *Vigabatrin*: This compound has been shown to be effective on all aetiologies of IS, in a double-blind trial comparing it to placebo (Appleton et al.,1999). In new onset cases, VGB monotherapy efficacy is greater in patients starting before the age of 3 months (over 90 per cent) than in those starting later (Aicardi et al.,1996). The rate of total suppression of spasms in newly diagnosed cases depends on aetiology. It is reached in 90 per cent in tuberous sclerosis and focal cortical dysplasia and 70 per cent in cryptogenic cases with no previous psychomotor delay. In this population, the success rate reaches 100 per cent when adding steroids in patients not responding to VGB monotherapy (Granstrom et al.,1999; Villeneuve et al.,1998). There seems to be a particular group of patients with psychomotor delay prior to the first spasms and no MRI abnormalities, who require the combination of both drugs to come under control, and a duration of treatment of more than 3 months in order to prevent relapse (Villeneuve et al.,1998). Side effects are mild, although frequent compared to those of steroids. They consist of irritability insomnia, agitation and weight gain. The issue of visual field defect is presently being considered, but to date, no child treated for IS in infancy has been shown to be symptomatic in that respect.
Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: Literature review. J Child Neurol 1999;14:71-4.	The purpose of this report is to review the efficacy and safety of vigabatrin in the treatment of infantile spasms in infants suffering from tuberous sclerosis complex. We reviewed all studies published in the English-language literature investigating the use of vigabatrin in the treatment of infantile spasms. Ten studies gave results for the efficacy of vigabatrin in infantile spasms for infants both with and without underlying diagnoses of tuberous sclerosis. Of the 313 patients without tuberous sclerosis complex, 170 (54%) had complete cessation of their infantile spasms; of the 77 patients with tuberous sclerosis complex, 73 (95%) had complete cessation of their seizures. We conclude that vigabatrin should be considered as first-line monotherapy for the treatment of infantile spasms in infants with either a confirmed diagnosis of

	tuberous sclerosis or those at high risk, ie, those with a first-degree relative with tuberous sclerosis complex. Paradoxically, in those without tuberous sclerosis complex, vigabatrin might be less efficacious than suggested by studies including patients with tuberous sclerosis complex.

Dulac O, Plouin P, Schlumberger E. Chapter 37 Infantile Spasms. In: Wyllie E, editor. The treatment of epilepsy: Principles and practice. 2nd ed. Baltimore: Williams & Wilkins;1997 : p.540-572. Ben-Menachen E. Chapter 69 Vigabatrin. In: Wyllie E, editor. The treatment of epilepsy: Principles and practice. 2nd ed. Baltimore: Williams & Wilkins;1997 : 906-12.	CHAPTER 37 Infantile Spasms OVERVIEW OF TREATMENT CONSIDERATIONS At this juncture, further research should take in account two important points: 1.**The search for specific indications based on etiology.** A first step has been to demonstrate that steroids are more effective in cryptogenic than in symptomatic WS(West syndrome) and that the reverse is true for vigabatrin. It may even be possible to delve more precisely into etiology. In symptomatic WS preceded by other types of sezures, steroids controlled spasms when first seizures indicated acute postnatal damage, but not when they were caused by brain malformation and were the initial expression of the epilepsy itself. TREATMENT INDICATIONS BASED ON ETIOLOGY **Symptomatic WS** **Prenatal Diseases** ***Malformations.*** In Aicardi's syndrome, nonsyndromic callosal agenesis, and other diffuse brain malformations, including hydranencephaly, holoprosencephaly, and lissencephaly, Is is resistant to a variety of drugs, including steroids. Valproate and low doses of benzodiazepines may moderately improve the seizure disorder. Hemimegalencephalic WS occasionally responds to vigabatrin or steroids. hemispherectomy is indicated by the end of the first year of life if seizures remain frequent, if indisputable hemiplegia is present, and if EEG and functional imaging scans demonstrete functional integrity of the contralateral hemisphere. West syndrome caused by focal dysplasia should be treated as are partial seizures with secondary generalization. Steroid therapy, corticectomy, and lobectomy have been variously effective. ***Neurocutaneous Syndromes.*** West syndrome secondary to tuberous sclerosis occasionally responds to steroids. In one series, 25% of patients benefited from benzodiazepines; in another series, from immunoglobulins. Nitrazepam in moderate doses (0.5 to 0.8 mg/kg per day) may be preferable to steroids because of better tolerability. Clonazepam may be tried in countries such as the United States where nitrazepam is not generally available.Most patients, however, are either resistant to these treatment or experience relapses. Vigabatrin may become the drug of choice for this disease. ***Virral Fetopathies.*** Presistence of viral infection contraindicates steroid therapy. Valproate, benzodiazepines, or vigabatrin may be useful. ***Vascular Disorders.*** West syndrome due to porencephaly or angioma may respond to steroid or vigabatrin, with favorable long-term outcome. Patients with frontal involvement seen more likely to have relapses. The uncapping procedure is indicated for persistent seizure. ***Anoxoischemic and Infectious Diseases.*** Steroid therapy usually controls WS. Sequelae of bacteria meningitis and of viral encephalitis by no means contraindicate their use. Immunoglobulins have proved helpful in occasional patients. Vigabatrin, lamotorigine, or valproate may be indicated in relapses. CHAPTER 69 Vigabatrin GENERAL CHARACTERISTICS MECHANISMS OF ACTION ABSORPTION,AND METABOLISM EFFICACY INTERACTIONS WITH OTHER DRUGS ADVERSE EFFECTS CLINICAL USE

Guideline for prescribing vigabatrin in children has been revised. BMJ 2000;320:1404-5.

Vigabatrin Paediatric Advisory Group.
Members of the group are:
Richard Appleton, consultant paediatric neurologist, Liverpool (to whom correspondence should be addressed at the Roald Dahl EEG Unit, Alder Hey Children's Hospital, Liverpool L12 2AP); Peter Baxter, consultant paediatric neurologist, Sheffield; David Calver, consultant ophthalmologist, London; Celia Cramp, consultant paediatrician, Shrewsbury; John Gibbs, consultant paediatrician, Chester; Graham Harding, consultant clinical neurophysiologist, Birmingham; John Livingston, consultant paediatric neurologist, Leeds; Richard Robinson, consultant paediatric neurologist, London; Isabelle Russell-Eggitt, consultant paediatric ophthalmologist, London; Sheila Wallace, consultant paediatric neurologist, Cardiff; and John Wild, senior lecturer in vision sciences, Birmingham.

EDITOR—In 1998 a paediatric advisory group in the United Kingdom produced a guideline to help clinicians when prescribing vigabatrin in children. The visual field defect reported in association with the drug has now been confirmed in five children treated with it. The paediatric guideline has now been revised and replaced with the one below, which reflects the current opinion of the advisory group.

- The defect is specific—a bilateral and concentric constriction that, within a 30° radius from fixation, consists of a nasal loss extending in an annulus over the horizontal midline, with a relative sparing of the temporal field. Its pathogenesis is thought to involve cone and amacrine cell dysfunction in the retina. The prevalence in adults is about 30%; that in children is not established. The relation between the duration of exposure to vigabatrin and the development of the field defect is not known. Neither recovery nor progression of the defect has been confirmed after withdrawal of the drug. Confrontation testing does not reliably identify the defect.
- Children with a cognitive age of ≥ 9 should undergo visual field examination with a Goldmann perimeter (11e or 12e isopter and 14e or V4e isopter) or a Humphrey field analyser (age related, three zone suprathreshold strategy and the 135 point field) before vigabatrin is prescribed and, ideally, every six months, particularly if they continue to take the drug.
- For children aged <9 a field specific visual evoked potential technique to assess peripheral vision is being evaluated in children with epilepsy but is not yet routinely available.
- Electroretinography performed according to international standards has shown abnormalities of cone function in adults and may be useful in children.

The continued prescription of vigabatrin remains one of risk versus benefit — the potential risk of the visual field defect developing against the potential benefit of seizure control. One specific risk is the implications of a field defect for driving in a patient with epilepsy who is seizure free.

- Children who have, or are at risk of developing, a visual defect due to other causes (for example, surgery) should be prescribed vigabatrin with caution. Children who are already registered blind, however, will have an altered risk:benefit ratio, possibly in favour of the drug. If the defect is identified the continued use of vigabatrin will depend on the overall clinical situation.
- Children taking vigabatrin whose seizures are well controlled should not automatically have the drug withdrawn. Current evidence suggests that the defect is unlikely to develop if perimetry gives normal results after more than three years of treatment.
- Vigabatrin remains the drug of choice for infantile spasms. Limited data suggest that it could be withdrawn without a relapse in infants who have been spasm free for six months.
- Other therapeutic indications include the treatment of children with partial epilepsy with or without secondary generalisation when other drug combinations have been ineffective or poorly tolerated. Vigabatrin seems to be particularly effective in children with seizures caused by tuberous sclerosis.
- Vigabatrin exacerbates typical absence and myoclonic seizures and should therefore not be prescribed in the idiopathic generalised epilepsies.

Revised guideline for prescribing vigabatrin in children. BMJ 2001;322:236-7.

Vigabatrin Paediatric Advisory Group.
Members of the group are: Richard Appleton, consultant paediatric neurologist, Liverpool (to whom correspondence should be addressed at the Roald Dahl EEG Unit, Alder Hey Children's Hospital, Liverpool L12 2AP); Peter Baxter, consultant paediatric neurologist, Sheffield; David Calver, consultant

Advisory group's reply

EDITOR—Both of Lux et al's letters (this one and that in 1999) have largely, and understandably, promoted the United Kingdom infantile spasm study; their comments have been of little relevance to both the initial[1] and revised[2] pragmatic clinical guideline. At the time that we wrote both guidelines, vigabatrin was the drug of first choice, on the basis of efficacy and safety evidence, in treating infantile spasms; it still remains the drug of choice.

We agree with Lux et al that there is no convincing evidence that vigabatrin shows superior efficacy to adrenocorticotrophic hormone or prednisolone either in controlling spasms or in long term neurodevelopmental outcome. It is disingenuous, though, to ignore the recognised benefits of using vigabatrin in treating infantile spasms-namely, that the drug seems to be effective in at least half of patients; that its

ophthalmologist, London; Celia Cramp, consultant paediatrician, Shrewsbury; John Gibbs, consultant paediatrician, Chester; Graham Harding, consultant clinical neurophysiologist, Birmingham; John Livingston, consultant paediatric neurologist, Leeds; Richard Robinson, consultant paediatric neurologist, London; Isabelle Russell-Eggitt, consultant paediatric ophthalmologist, London; Sheila Wallace, consultant paediatric neurologist, Cardiff; and John Wild, senior lecturer in vision sciences, Birmingham.	effect is rapid (usually less than seven days in patients responsive to vigabatrin); and that, unlike adrenocorticotrophic hormone and prednisolone, it does not cause severe side effects. The information currently available on visual field constriction does not alter this opinion, the reasons for which have been discussed recently in more detail.[2] With these issues in mind, the justification for the content of the pragmatic guideline should be obvious. Although we support Lux et al's call for large and well designed comparative studies, methodological and ethical concerns about their study have precluded universal participation in it. Roughly 300 British children develop infantile spasms each year. For these children, their parents and carers, and their clinicians, treatment cannot be deferred pending the findings of the United Kingdom study, whose results will not be available for many years. In addition, because infants who have infantile spasms (and West's syndrome) do not constitute a homogeneous population, the study findings may prove inconclusive. In the interim the guideline simply provides clinicians with pragmatic advice about how and when to use vigabatrin in the paediatric epilepsies, including infantile spasms. We should emphasise that our opinion is shared by many paediatric neurologists outside the United Kingdom, including paediatric neurologists in the United States (personal communication).
Aicardi J, Sabril IS Investigator and Peer Review Groups, Mumford JP, Dumas C, Wood S. Vigabatrin as initial therapy for infantile spasms: A European retrospective survey. Epilepsia 1996;37(7):638-42.	PURPOSE: 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. METHODS: Our retrospective study included 250 infants diagnosed with IS; the data obtained were subjected to peer-group review. Of this infant population, 192 infants were considered to have classic IS and had received VGB as their first treatment for the spasms. There was a slight preponderance of boys (57%) in this population. Mean age of IS onset was 5.8 months; 60% had typical hypsarrhythmia. 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. Treatment appeared to be well tolerated, with only 33 (13%) infants with adverse events, of which the most common were somnolence (15 patients) and hyperkinesia (eight patients). In only two cases did adverse events require VGB withdrawal. CONCLUSION: This study supports the opinion that VGB may be considered an initial treatment for IS regardless of cause.

5－2．エビデンスとして重要な論文名と記載内容（カテゴリーについては適宜変えて可）

対象とする年齢の小児の PK データ

著者、雑誌名、ページ、発行年など	記載内容のサマリー
Rey E, Pons G, Richard MO, Vauzelle F, D'Athis P, Chiron C, et al. Pharmacokinetics of the individual enantiomers of vigabatrin (gamma-vinyl GABA) in epileptic children. Br J Clin Pharmacol 1990;30:253-7.	1. The pharmacokinetics of the enantiomers of vigabatrin were investigated after oral administration of a single 50 mg kg-1 dose of the racemate to two groups of six epileptic children (I: 5 months-2 years, II: 4-14 years). 2. The mean (+/- s.d.) values of maximum plasma concentration and area under the plasma concentration-time curve of the R(-) enantiomer were significantly higher than those of S(+) vigabatrin in both groups: R(-) Cmax: 21 +/- 6.6 (I)-41.3 +/- 13.9 (II) vs S(+) Cmax: 13.9 +/- 4.5 (I)-23.8 +/- 12.2 (II) mg l-1; R(-) AUC: 106 +/- 28.5 (I)-147 +/- 34 (II) vs S(+) AUC: 90.9 +/- 27.9 (I)-117 +/- 26 (II) mg l-1 h. In group I, the half-life of the R(-) isomer was significantly shorter than that of the S(+) isomer; in group II, the half-lives were comparable. 3. For the R(-) enantiomer the area under the curve, and the elimination half-life increased linearly with age. 4. During chronic administration (50 mg kg-1 vigabatrin racemate twice a day for 4 days), the morning trough plasma drug concentrations did not increase.
Grant SM, Heel RC. Vigabatrin A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Epilepsy and Disorders of Motor Control. Drug 1991;41(6):889-926.	2. Pharmacokinetic Studies 2.4 Effect of Age 2.4.1 Children A single 50 mg/kg oral dose of Vigabatrin was administered to a group of infants (mean age 12.1 months) and a group of 6 children (mean age 8.7 years) with uncontrolled seizures (Rey et al. 1990). A significant effect of age was noted only for the

	pharmacologically inactive R- enantiomer for which the AUC and t1/2β increased linearly with age. As in adults, the Cmax of S-vigabatrin was approximately 2-fold lower than that of R-vigabatrin, but neither the Cmax nor the t1/2β of S-vigabatrin differed according to age in these 2 groups. Renal clearances for both enantiomers (calculated in 5 patients) were similar to those reported in adults, but area under the plasma concentration-time curve was lower which suggests that bioavailability in children may be lower. Thus, a reduced dosage does not appear to be necessary in children > 1 month of age (Rey et al. 1990), and, andeed, dosagea of ≥ 100 mg/kg/day may be needed to achieve the desired synaptic concentrations of vigabatrin (personal communiocation, Prof Dukac).
Ray E, Pons G, Olive G. Vigabatrin Clinical Pharmacokinetics. Clin Pharmacokinet 1992;23(4):267-78.	4.1 Children With Epilepsy The pharmacokinetics of the enantiomers of Vigabatrin were investigated after oral administration of a single 50 mg/kg dose of [R,S]-vigabatrin to 2 groups of 6 children with epilepsy (group I aged 5 months to 2 years, group II aged 4 to 14 years) [Rey et al.1990]. A significant effect of age was noted only for the pharmacologically inactive R(-)enantiomer for which the AUC and the elimination half-life increased linearly with age. The Cmax of S(+) vigabatrin was 2-fold lower than the R(-) form. The half-life [group I :S(+) 3.7 to 8.3h, R(-) 2.6 to 11h; group II :S(+) 3.9 to 8.7h, R(-) 1.8 to 4.5h] was similar to that in adults except for the half-life of R(-), which was shorter in infants. The AUC was lower in these 2 groups than in adults, which suggested a lower bioavailability as renal clearance values for both enantiomers (CL_R:0.059 to 0.187 L/h・kg for R(-) and 0.031 to 0.120 L/h・kg for S(+); n=5) were similar to those reported in adults. Plasma concentration measurement during multiple-dose administration (5 days) showed no accmulation of either enantiomer. Due to the short half-life of the drug, steady-state was achieved within the 5 days.
Battino D, Estienne M, Avanzini G. Clinical Pharmacokinetics of Antiepileptic Drugs in Paediatric Patients. Clin Pharmacokinet 1995;29(5):341-69.	[Absorption and Bioavailability] Vigabatrin is rapidly absorbed by the gastrointestinal tract. Absorption is more rapid and more complete in older than in younger children; this difference reflected in the bioavailability of the drug, since the AUC is significantly greater in older children. In contrast to adults, in whom the tmax of the R(-)-enantiomer of vigabatrin is about twice that of the active S(+)-enantiomer, no differences were found in the tmax of the 2 allosteric forms in children. The mean Cmax of the R(-)-enantiomer always exceeded that of the active S(+)-enantiomer; the tmax was similar for both isomers. The mean AUC of the R(-)-enantiomer was also significantly greater than that of the S(+)-enantiomer. The AUC values for each isomer are significantly lower in infants than in children, which in turn are lower than in adults. The mean R(-)/S(+)-enantiomer Cmax ratios were 1.6 and 1.8 in children with epilepsy aged 5 months to 2 years and 4 to 14 years, respectively. The plasma concentration of both enantiomers was similar at 6 and 24 hours after administration. During the long term administration of Vigabatrin 50 mg/kg twice daily, mean morning fasting plasma concentrations varied from 2.0 to 3.8 mg/L for the R(-)-enantiomer and from 1.5 to 3.0 mg/L for the S(+)-enantiomer. There is no accumulation of either of the Vigabatrin enantiomers, evidence for this being that the mean moring plasma concentrations of both do not significantly increase over a 4-day period. The plasma concentrations of Vigabatrin at 1 hour postdose also show no signs of an increase over 4 days. One hour after administration, mean plasma concentrations varied 10.3 to 17.4 mg/L for the R(-)-enantiomer and from 16.0 to 28.0 mg/L for the S(+)-enantiomer.
二重盲検等の対照薬を用いた比較試験	
著者、雑誌名、ページ、発行年など	記載内容のサマリー
Appleton RE, Peters AC, Mumford JP, Shaw DE. Epilepsia 1999 ; 40(11):1627-33.	Double-blind, placebo-controlled, parallel-group study. 対象：Infantile spasm 40 例（各群 20 例）、投与期間：5 日間。 【成績】50%以上の発作頻度減少：ビガバトリン 78% vs プラセボ 26%（p=0.020）。 発作消失：ビガバトリン 7 例 vs プラセボ 2 例 (p=0.063)。有害事象による脱落例なし。 PURPOSE: Vigabatrin (VGB) has been shown to be an effective drug in the treatment of infantile spasms (West syndrome) in predominantly retrospective and open but also in prospective studies. 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. METHODS: 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 ($p = 0.020$). Seven VGB-treated patients and two placebo-treated patients were spasm free on the final day of the double-blind period ($p = 0.063$). 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. No patient withdrew from the study because of an adverse event. CONCLUSIONS: This unique randomized, placebo-controlled study is the first to demonstrate the efficacy of a specific drug in the treatment of West syndrome and supports the results of previously published open and prospective trials. It further confirms that VGB could be considered as the drug of first choice in treating infantile spasms.
Chiron C, Dumas C, Jambaque I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res 1997;26:389-95.	A randomized study has shown better effect of vigabatrin than steroids in infantile spasms due to tuberous sclerosis. Vigabatrin has been shown to be efficient in infants with infantile spasms and tuberous sclerosis, in open studies. 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. All vigabatrin patients (11/11) were spasm-free versus 5/11 hydrocortisone infants ($P < 0.01$). 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 ($P < 0.01$). Five patients exhibited side effects on vigabatrin but nine on hydrocortisone ($P = 0.006$). Vigabatrin should therefore be considered as the first choice treatment for infantile spasms due to tuberous sclerosis.
Appleton RE. The role of vigabatrin in the management of infantile epileptic syndromes. Neurology. 1993 Nov;43(11 Suppl 5):S21-3.	More than 360 children with intractable epilepsy have been treated with vigabatrin in single-blind or open, add-on studies. Approximately 50% or more of patients with West syndrome and partial seizures have shown a 50% or greater reduction in seizure frequency with the use of vigabatrin. A less consistent response has been found between studies evaluating vigabatrin in children with Lennox-Gastaut syndrome, although, overall, approximately 50% of these patients have also shown a greater than 50% decrease in seizures. The use of vigabatrin in idiopathic localization-related epilepsy, idiopathic generalized epilepsy, and the Landau Kleffner syndrome have not been reported, but its evaluation in these conditions may be warranted based on the relatively excellent safety profile of vigabatrin. Vigabatrin has been shown to aggravate "nonprogressive myoclonic epilepsies." Vigabatrin has been well tolerated in children, with mild drowsiness and agitation being the most commonly reported side effects.
Appleton RE, Montiel-Viesca F. Vigabatrin in infantile spasms -- why add on? Lancet 1993;341(8850):962.	Double-blind study against placebo. Sir,—Corticosteroids, the currently recommended drugs for the treatment of infantile spasms, are frequently associated with serious side-effects. Vigabatrin is effective as add-on therapy in intractable infantile spasms, especially in those of symptomatic origin. In view of these preliminary data and the impressive safety profile of vigabatrin, we have used this drug as the initial monotherapy in infantile spasms over the past 18 months. Permission for the study was obtained from the local ethical committee. 15 children (aged 3-11 months) presented with infantile spasms, of between 2 and 10 (mean 5) weeks' duration.Hypsarrhythmia was recorded on the electroencephalograms of all 15, and development was delayed in 13. 10 were classified as symptomatic, 3 as cryptogenic, abd 2 as idiopathic (with normal development). Aetiology in the 13 patients with symptomatic spasms induced cerebral dysgenesis, neonatal

	hypoxicischaemic encephalopathy, perinatal periventricular haemorrhage, and astrocytoma. No patient had tuberous sclerosis. Vigabatrin was started at diagnosis at 50-80 mg/kg per day, increasing over 3 days to a maximum of 100-150 mg/kg daily. In 4 patients spasms ceased within 72 h of starting treatment and these patients have remained seizure-free for 3-20 months. 7patients had an initial reduction in spasms of between 75 and 100% (within 72 h) but relapsed after 4-6 months. However, only 1 of these patients had a total relapse and subsequent control has been difficult (responded to sodium valproate and nitrazepam but not to corticosteroids). In the remaining 4 (of the entire group), the spasms were unaltered and other treatments were introduced after 5 days, with limited success. No adverse effects have been observed and follow-up is currently 3-20 (mean 11) months. In the 4 patients with complete and sustained contrl, no other seizure type has developed. There were no aetiological, clinical, or electroencephalographic features to distinguish responders from non-responders, but this probably reflects the small number of patients. Although corticosteroids may produce short-term control of spasms, they have not been shown conclusively to improve long-term outcome (development of late epilepsy or mental retardation), and relapses are common whether on or off treatment. The excellent safety profile of vigabatrin compared with corticosteroids suggests that vigabatrin should be considered as the preferred drug for the treatment of spasms. Ours was a small group of patients, but the results were promising. In addition, the drug works rapidly (within 3 days) and there is no need to escalate the dose, because there does not appear to be any significant does-response relation, at least in older children. If there has been no response to vigabatrin after 4-5days, the drug can be replaced. It is unlikely that any delay of 4-5 days would affect the short-term or long-term outcome.
Chiron C, Dulac O, Luna D, Palacios L, Mondragon S, Beaumont D, Mumford JP. Vigabatrin in infantile spasms. Lancet. 1990;335(8685):363-4.	Single-blind study Sir,—The anti-epileptic efficacy of vigabatrin (gamma-vinyl GAVA) is especially high patients with partial complex seizure. We have recently completed a single-blind study of vigabatrin in 61 children with refractory epilepsy. Infantile spasms (IS) is a unique epileptic syndrome affecting infants during the first year of life. It is one of the most refractory types of epilepsy and carries a poor prognosis. The most effective treatment is steroids, but side-effects are common, efficacy is often transient, and whether there are long-term benefits is controversial. Results vary but a recent prospective series showed that 48% of children had a long-term response. Efficacy of other anti-epileptic drugs such as the benzodiazepines or valproate is less striking though they are better tolerated. We have now had the opportunity to observe the efficacy of vigabatrin on 45 children aged 2 months to 10 years (mean 26months) with drug-resistant IS. According to Glaze et al, 27 of these children could be classified as having cryptogenic IS; the remaining 18 had symptomatic IS, including 8 children with tuberous sclerosis. All were resistant to previous treatment, including corticosteroids (hydrocortisone) (28 patients) and benzodiazepines or valproate. Before the start of Vigabatrin therapy spasms had been present for between 0.5 and 145 months (mean 22). The mean frequency of spasms was about 130 per months. 14 patients also had partial seizures. Concomitant medication ranged from 1 to 3 other drugs (mean 1.8). We could not evaluate the efficacy of Vigabatrin in 3 patients since the drug was discontinued because of hypotonia in 1, hypertonia in 1, and hyperexcitability in 1 soon after the start of treatment. The remaining 42 children have now been treated with vigabatrin 50-200 mg/kg daily for 4-24 months (mean 9.5). A greater than 50% reduction in spasms was obtained in 30 patients (71%) and complete suppression from the onset of vigabatrin in 16 (38%). Concomitant anti-epileptic drugs were reduced in 15, and 7 are now on vigabatrin monotherapy. Better results were seen when vigabatrin treatment had been started earlier in the course of the disease—where spasms had been present for less than a year, 13 of 25 patients responded, compared with only 3 of the 17 who had had spasms for over a year. Perhaps the most striking finding was the response to vigabatrin in relation to the aetiology of Is. A much better effect was seen in symptomatic IS, with 11 (69%) of 16 showing complete control compared with only 5 (19%) of 26 with cryptogenic IS.

	This response was further confirmed in the children who also had tuberous sclerosis −7 of 8 had complete suppression of their spasms. Control seemed to be transient in 6 of the cryptogenic cases following an initial sezure-free period of 3-12 months, whereas seizure control has been maintained so far in all symptomatic cases (mean follow-up 15 months). Apart from the 3 children from whom vigabatrin was withdrawn, most patients tolerated the drug well, with only mild and transient adverse events being reported in 9 (hyperkinesias, weight gain, drowsiness). These preliminary findings suggest that vigabatrin is potentially very valuable in the management of intractable IS, especially when they are associated with tuberous sclerosis, since this condition is known to have a very poor prognosis.
その他の試験（国内における公的研究費による委託研究などがある場合は、どのような委託研究によって行われたかも必ず記入）：該当なし	
著者、雑誌名、ページ、発行年など	記載内容のサマリー
6．臨床現場での必要性と、なぜ開発が行われていないのか	
臨床現場の必要性	現在、点頭てんかんにおいてはACTH療法以外に適当な治療法はなく、既存の抗てんかん薬では十分な効果が得られていないのが現状である。ACTH療法においては、副作用（免疫力低下、脳退縮等）の問題で長期使用が難しいこと、効果が長続きしないこと、知的発達の長期予後の観点からみると改善が認められないことなどが指摘されている。 点頭てんかんに有効性が認められた数少ない薬剤ということで、専門医及び患者団体（日本てんかん協会）より強い要望があり、現状では個人輸入により使用されている。
開発が行われなかった理由	視野狭窄の発現頻度が約30%という状況から、国内における成人での効能・効果取得を断念し、現在開発中断の状況にある。
7．どのような開発が適切であると考えられるか	
開発へのアプローチ	その根拠
小児の点頭てんかんのみを対象としたオーファンドラッグとしての開発を進める。	成人の難治性てんかんにおいて二重盲検比較試験において約50%（中等度改善以上）の成績が得られ、抗てんかん薬としての有効性が確認されたものの、視野狭窄の問題より成人における効能・効果取得は困難と判断した。しかし、小児の点頭てんかん（West症候群）に関しては、既存及び現在開発中の抗てんかん薬の中にも有効とされる薬剤は見当たらない。海外においても視野狭窄という有害事象の問題はあるもののリスク/ベネフィットを考慮し使用されている現状を考えると、本邦においても治療の一手段として医療現場に提供すること必が要と考える。その際には、限られた効能かつ専門医師による使用が適当と考える。
8．現在までの働きかけとそれに対する反応		
誰（どこ）が	誰（どこ）に	どのような働きかけをしたかと、それに対する相手の反応、進行状況