



MHRA PUBLIC ASSESSMENT REPORT

Vigabatrin use: risk of movement disorders and brain MRI abnormalities

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EXECUTIVE SUMMARY

(Please note that this summary is intended to be accessible to all members of the public, including health professionals)

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports, we discuss the scientific and clinical evidence for a safety issue with a particular drug or drug class, and, any changes made to product information for a medicine on the basis of this evidence, to help safeguard public health. This MHRA Public Assessment Report discusses the risk of movement disorders^a and abnormalities seen in magnetic resonance imaging (MRI)^b scans associated with a medicine called vigabatrin.

Vigabatrin is used to treat epilepsy^c and a condition called infantile spasms or West's syndrome (epilepsy in infants). Vigabatrin was licensed in 2001 and is marketed in the UK under the brand name Sabril.

As with any medicine, the use of vigabatrin may lead to side-effects in some individuals, which are described in the patient information leaflet accompanying the medicine and on the [Electronic Medicines Compendium \(product information\) website](#). Recent reports suggest that the use of vigabatrin to treat infantile spasms may be associated with movement disorders and abnormalities in brain MRI scans in these patients. A review completed in July, 2009 assessed the evidence available on this issue, including data from research studies performed before clinical trials in humans, data from clinical trials, reported cases of side-effects (adverse drug reactions [ADRs]) and published literature. This Public Assessment Report presents a summary of the data and the conclusions of the review.

Results

There were 18 reports of movement disorders identified in clinical trials with vigabatrin (research studies performed before vigabatrin was licensed and marketed), and 58 worldwide reports of movement disorders identified after vigabatrin was licensed. Six European cases of MRI abnormalities were reported in infants treated with vigabatrin after it was licensed, of which four cases also reported movement disorders. Twelve cases of MRI abnormalities with vigabatrin use were reported worldwide after licensing. In one published study, 17/79 (22%) of infants treated with vigabatrin for infantile spasms had abnormal MRI scans, compared with 4/98 (4%) of infants with infantile spasms who received other treatments.

Conclusions

Clinical trial data and published literature provide evidence that brain MRI abnormalities are seen in infants treated with vigabatrin for infantile spasms. In addition, ADR reports suggest that movement disorders may also occur in patients treated with vigabatrin. Based on these data, a warning on the risk of movement disorders and brain MRI abnormalities associated with vigabatrin use in patients with infantile spasms will be included in the product information.

^a A range of conditions characterised by abnormal body movements

^b A machine that shows the internal structure of the body on a screen

^c A brain condition characterised by fits or seizures

1. INTRODUCTION

(See glossary for explanation of terms used in this document)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports, we discuss the scientific and clinical evidence for a safety issue with a particular drug or drug class, and, any changes made to product information for a medicine on the basis of this evidence, to help safeguard public health. This MHRA Public Assessment Report discusses the risk of movement disorders and abnormalities seen in magnetic resonance imaging (MRI) scans associated with a medicine called vigabatrin.

Vigabatrin (Sabril) is an antiepileptic indicated, in combination with other antiepileptic drugs, for the treatment of patients with resistant partial epilepsy (with or without secondary generalisation) who have not responded to, or who are intolerant to, all other appropriate drug combinations. Vigabatrin is also indicated as monotherapy in the treatment of infantile spasms (West's syndrome).

Finland raised concerns about the risk of movement disorders and brain abnormalities on MRI (interpreted as cytotoxic oedema) associated with the use of vigabatrin, after they received reports of these adverse drug reactions (ADRs).

A Europe-wide review completed in July, 2009 assessed the evidence available on this issue, including preclinical data, clinical data, reported cases of ADRs and relevant published literature. This Public Assessment Report presents a summary of the data and the conclusions of the review.

2. SUMMARY OF AVAILABLE DATA

2.1 Preclinical data

High doses of vigabatrin induced intramyelinic oedema and microvacuolation in specific areas of brain white matter in rodents and dogs. The microvacuoles seemed to be the result of fluid accumulation and separation of the outer layers of myelin. The findings partially or completely reversed on cessation of vigabatrin (see section 5.3 of [Sabril SPC](#)).

2.2. Clinical Trial data

From the clinical trial data, eighteen cases of movement disorders were identified. The movement disorders included reports of hyperkinesia, dyskinesia, clumsiness, extrapyramidal disorder, and hypertonia. Thirteen patients were followed up (whose movement disorder types were not specified); seven of whom recovered while still continuing to take vigabatrin.

There were no cases in the clinical trials database that described MRI changes associated with the use of vigabatrin.

2.3 Case reports received after licensing – European data^a

Six European reports of MRI abnormalities with vigabatrin use were received from November 2005 to April 2007. Four of these cases also reported movement disorders relating to abnormalities in muscle tone, including dystonic reactions, increased tone and spasticity cases.

In these cases it is unclear how well the movement disorders correlate with the abnormal MRI findings. MRI changes are also associated with the use of adrenocorticotrophic hormone and steroids, and may be associated with underlying brain pathology or changes related to metabolic errors at birth which can further complicate the interpretation of the MRI findings reported in these cases.

From these six case reports it may be concluded that abnormalities of muscle tone including dystonia and spasticity have been reported in association with vigabatrin use and that these abnormalities have occurred in some patients who have also had abnormal MRI findings. The abnormalities in muscle tone all resolved when vigabatrin was ceased, and the MRI abnormalities also resolved in three cases after stopping vigabatrin treatment, two of which cases also reported movement disorders that resolved on ceasing vigabatrin. It is unknown whether the MRI scans returned to baseline in the three other case reports after stopping vigabatrin treatment.

^a Suspected adverse drug reactions to any medicine in the UK can be reported to the MHRA through our [Yellow Card Scheme](http://yellowcard.mhra.gov.uk) (<http://yellowcard.mhra.gov.uk>)

2.4 Case reports received after licensing – worldwide data.

Over fifty worldwide cases of movement disorders and/or MRI abnormalities were reported with vigabatrin use after it was licensed and marketed, including: brain oedema; abnormal brain scan; demyelination; muscle twitching; dyskinesia; dystonia; hypertonia; movement disorder; hyperkinesia; tardive dyskinesia; opisthotonus; akathisia; akinesia; clumsiness; and head titubation.

2.5 Cumulative review

The marketing authorisation holder^a conducted its own review of cases of movement disorders and MRI abnormalities, which identified 23 reports of abnormal brain MRI and brain oedema.

Two of the cases of brain oedema can be explained by concomitant disease (glioma and medulla oblongata haemorrhage).

The cases describing 'brain scan abnormalities' are from the early 1990s when MRI scanning was not widely available and the indication for vigabatrin use differed. None of these cases relate to patients treated for infantile spasms and none of the cases are associated with any movement disorder.

From the cumulative review data it is significant that in more than half of the cases where outcome data was recorded, the MRI abnormalities resolved despite continuing vigabatrin.

^a Person or company responsible for placing a medicinal product on the market (usually the product manufacturer)

3.0 PUBLISHED LITERATURE

3.1 Wheless J et al, 2009¹

This retrospective, multicentre, cohort comparative epidemiological study estimated the prevalence and incidence of MRI abnormalities in infants with infantile spasms who were treated with vigabatrin compared to those given other treatments. However, the study was not designed to investigate the relationship between the MRI abnormalities and any movement disorders, or other clinical associations of the abnormal MRI findings.

Results

Medical records and 332 cranial MRIs from 205 infants (aged 24 months or younger) with infantile spasms treated at ten sites in the US and Canada were identified for inclusion in the study.

At all doses of vigabatrin

Of the 205 infants in the study, 93 received vigabatrin treatment, and 112 received treatment other than vigabatrin.

In a study sub-group called the prevalence population, the prevalence of MRI abnormalities was examined, defined (here) as the occurrence of at least one MRI abnormality during the treatment period.

The prevalence population comprised 177 patients; 79 of whom were treated with vigabatrin, and 98 of whom did not receive vigabatrin. The prevalence of abnormal MRIs was significantly higher in the vigabatrin-treated group (17/79 [22%]), compared with the group not treated with vigabatrin (4/98 [4%]; $p < 0.001$). The risk of developing MRI abnormalities with vigabatrin with respect to prevalence was 13.6% (95% confidence interval [CI]: 3.8–23.4%).

Of the 79 patients in the prevalence population exposed to vigabatrin, nine had a prespecified MRI abnormality and at least one subsequent determinate MRI. The MRI abnormalities resolved in six of these nine patients – in two patients the MRI abnormalities resolved during vigabatrin treatment and in four patients after discontinuing vigabatrin.

A second study subgroup called the incidence population aimed to capture the incidence of all cases where MRI changed from normal to abnormal during the study. Patients included in the incidence population had a baseline MRI scan that was free of abnormalities and one postbaseline MRI scan.

The incidence population comprised 42 patients; 25 of whom were treated with vigabatrin and 17 of whom did not receive vigabatrin. In the incidence population, the incidence of prespecified MRI abnormalities was significantly higher in the vigabatrin-treated group (9/25 [36%]) than in the group not treated with vigabatrin (1/17 [6%]; $p = 0.031$). The risk of developing MRI abnormalities with vigabatrin with respect to incidence was 30.1% (95% CI: 8.2–52.0%).

Of the 25 patients in the incidence population exposed to vigabatrin, four had a prespecified abnormality and at least one subsequent determinate MRI. The MRI abnormalities returned to baseline in three out of these four patients; in one during vigabatrin treatment and in two after discontinuing vigabatrin.

Comparing low and high dose vigabatrin

In this study, low-dose vigabatrin was defined as <125 mg/kg/day and high-dose vigabatrin was defined as ≥125 mg/kg/day.

In the prevalence population, 4/32 patients (13%) had an abnormal MRI on low-dose vigabatrin compared with 13/44 patients (30%) on high-dose vigabatrin.

In the incidence population, 4/12 patients (33%) had an abnormal MRI on low-dose vigabatrin, compared to 5/12 patients (42%) on high-dose vigabatrin.

Study Conclusions

The study investigators concluded that vigabatrin is associated with asymptomatic MRI abnormalities characterised by increased T2 weighted signal in infants with infantile spasms. If MRI abnormalities occurred the investigators stated they were transient, appeared to be dose-dependent, and the majority resolved even if treatment with vigabatrin was continued.

Summary:

The study provides evidence that vigabatrin is associated with MRI abnormalities in infants treated for infantile spasms – these MRI findings appeared largely transient, asymptomatic and dose-dependent, and the majority resolve despite continuation of treatment. A relative risk of 5–6 fold higher than that associated with exposure to other infantile spasm treatments was estimated from the data in this study but the confidence intervals were wide.

The study was not designed to investigate the correlation between movement disorders and MRI abnormalities. The finding of a dose-response for the incidence and prevalence of MRI abnormalities is significant but numbers in the individual high and low dose groups were small (n=12 for both dose groups in the incidence population; n=32 and 44, respectively, for the low-dose and high dose groups in the prevalence population). Median times from the first treatment of infantile spasms to the first MRI signal abnormality could not be accurately determined because of the irregular frequency of MRI examination; however, among patients treated with vigabatrin the median time to detection of MRI abnormality of 11 months in the high dose group, and 24 months in the low dose group further suggests a dose effect; ie, the incidence and prevalence appeared to increase with dose.

The findings from this study are consistent with previous reports and case reviews from single institutions that vigabatrin-associated MRI abnormalities occur in 10-20% of treated patients². The significance of the MRI findings is still uncertain especially as the anatomical areas of the MRI abnormalities are also common sites of MRI abnormalities reported with metabolic errors at birth³. Considering a high proportion of infantile spasms are from unknown causes, it cannot be excluded that these transient MRI abnormalities may have an as yet unidentified metabolic cause.

3.2 Other relevant published literature

Desguerre³ et al 2003 reported T2 weighted hyperintensity in the basal ganglia of three patients with infantile spasms treated with vigabatrin. The abnormalities, which were present prior to treatment, were presumed to be a possible cause (mitochondrial disorder) of the infantile spasms.

Chiron⁴ et al (1989) reported normal MRI findings in children exposed to therapeutic doses of vigabatrin for an average of 11 months.

A large review (412 patients) cited in Cohen⁵ et al, 2000 did not identify any definite cases of intramyelinic oedema in humans treated with vigabatrin but it is unclear whether infants were included.

In 2008, Desguerre⁶ reported transient MRI diffusion study abnormalities in West syndrome in 5 patients with infantile spasm imaged at a mean age of 13 months with follow up 6 to 18 months later. All patients were treated with vigabatrin at the time of the first and follow up scan and the scan results resolved despite the patients remaining on the drug. The mean dose of vigabatrin was 100mg/kg/day on the initial MRI scan as opposed to 61mg/kg/day at the second scan. The authors did not attribute the MRI scan change to vigabatrin. Pre vigabatrin scans were not available.

The MRI abnormalities in Pearl et al 2009⁴, seemed to occur only in infants with infantile spasms, on higher doses of vigabatrin (out of a total of 22 patients in the study). The majority of infantile spasm patients in this study with MRI abnormalities did not show clinical worsening. Uncontrolled movement disorders were not seen and all MRI abnormalities showed resolution upon withdrawal of therapy.

4.0 CONCLUSIONS

Clinical trial data from the literature¹ provides evidence that brain MRI abnormalities are observed in infants treated with vigabatrin for infantile spasms. The MRI abnormalities observed in the published study appeared to be dose dependent and were transient in the majority of patients, resolving even in those who remained on vigabatrin. Data from case reports are less robust here.

Currently, there are no data that prove a direct correlation between exposure to vigabatrin and development of movement disorders associated with MRI changes (suggesting cytotoxic oedema) that shows a clear resolution of both movement disorders and MRI changes upon discontinuing treatment. The reported data are conflicting and the largest available study to date¹ was not specifically designed to investigate the correlation of movement disorders with MRI abnormalities. However, there is sufficient evidence from the reported cases that movement disorders may also occur in patients treated with vigabatrin. From the data assessed it seems likely that these movement disorders occur in children treated with vigabatrin for infantile spasms and in older patients treated with vigabatrin for other indications.

It may not be possible to correlate the MRI findings with movement disorders until there is a prospective study designed to document both occurrences of movement disorders and associated changes in the post treatment MRI scans of patients on vigabatrin, and to compare these outcomes to patients with infantile spasms who are not treated with vigabatrin. It was therefore decided that the two events “movement disorders” and “MRI abnormalities” should be independently described in the product information for vigabatrin.

Paediatric neurological experts from the UK have advised that it is preferable to describe the exact MRI changes mentioned in the studies. Although the MRI abnormalities found with diffusion weighted imaging and apparent diffusion coefficient mapping suggest cytotoxic rather than vasogenic oedema it is felt that the neuropathology underlying these observed MRI changes is unknown. Children treated with vigabatrin appear to develop these MRI changes without associated neurological deterioration in the majority of the cases and the changes may resolve even if vigabatrin is continued. It was therefore considered inappropriate to suggest that children should be ‘screened’ with repeated MRI scans while taking vigabatrin.

In rare cases where patients taking vigabatrin develop maintained neurological deterioration, especially movement disorders or dystonia, it would be reasonable to perform an MRI scan to look for an underlying cause of the deterioration. In such cases it also seems appropriate to consider reducing the dose or stopping vigabatrin; however this would need careful consideration, because of the risk of deterioration in seizure control.

Thus, on basis of the available data, the risk of movement disorders and brain MRI abnormalities with vigabatrin will be kept under close review and the product information, both the SPC and the patient information leaflet, will be updated with the following text:

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Cases of abnormal brain MRI findings have been reported, in particular in young infants treated for infantile spasms with high doses of vigabatrin. The clinical significance of these findings is currently unknown.

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

Section 4.8 Undesirable effects

Nervous system disorders
Frequency: Not known

Cases of brain MRI abnormalities have been reported (see section 4.4).

Movement disorders, including dystonia, dyskinesia and hypertonia have been reported, either alone or in association with abnormalities in MRI (see section 4.4).

Patient Information Leaflet

Section 2. Take special care with...

Movement disorders have been seen in young infants treated for infantile spasm (West syndrome). If you observe movement disorders in the child, consult the doctor who will decide if it is necessary to consider changing the treatment

Section 4. Possible side effects

Side effects with unknown frequency:

Movement disorders in young infants treated for infantile spasm

5.0 REFERENCES

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2. Pearl et al. Diagnosis and treatment of neurotransmitter disorders *Curr Treat Options Neurol* 2006; **8**: 441–450
3. Desguerre I et al. Infantile spasms with basal ganglia MRI hypersignal may reveal mitochondrial disorder due to T8993G MT DNA mutation. *Neuropediatrics* 2003; **34**:265–269
4. Pearl P et al. Cerebral MRI abnormalities associated with vigabatrin therapy. *Epilepsia* 2009; **50**(2):184–194
5. Chiron C et al. Vigabatrin in infantile spasms. *Lancet* 1990; **335**:363–364
6. Cohen et al. The potential for vigabatrin-induced intramyelinic oedema in humans. *Epilepsia* 2000; **41**:148–157
7. 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**:112–116

6.0 GLOSSARY

Adrenocorticotrophic hormone

A chemical made and stored in the brain which is released in response to stress

Akathisia

Involuntary body movements

Akinesia

A loss of normal muscle responses

Apparent Diffusion Coefficient Mapping

An MRI technique

Asymptomatic

Without symptoms

Cerebellum

The largest part of the rear of the brain, essential for muscle tone and balance

Clinical trial

A research study that tests new medicines on humans

Concomitant

Two or more medicines given or taken at approximately the same time (eg, one after another on the same day)

Confounds/confounding/confounded

Where the presence of one **risk factor** changes the effects that another risk factor has on the development of a medical condition; this can affect the results of a study

Correlate/correlation

A statistical term that shows by how much one characteristic can affect another in an individual.

Cranial

In the skull

Cytotoxic oedema

Swelling of cells in the body, and spaces between cells

Demyelination

Loss of the **myelin** covering of nerve fibres; this impairs nerve function

Diffusion Weighted Imaging

An MRI method

Dyskinesia

Involuntary repetitive bodily movements caused by an underlying medical disorder

Dystonia

Abnormal muscle contractions

Glioma

A tumour of **glial cells** in the nervous system

Glial cells

Supportive connective tissue in the nervous system (not composed of nerve cells)

Haemorrhage

Internal or external bleeding from a burst blood vessel

Hyperkinesia

Overactive restlessness

Hypertonia

High tension in muscles

Hypothalamus

A region of the brain that controls body temperature, thirst and hunger

Incidence

The number of new episodes of an illness or medical condition occurring in a specific population of people over a specific period of time

Intramyelinic oedema

Swelling of the **myelin sheath** of nerve cells

Median

A statistical average

Medulla oblongata

The lowest part of the brainstem which controls breathing, heart rate and blood pressure

Metabolic errors

Inability of the body to break down certain substances or make new essential ones (because of an underlying medical condition)

Microvacuolation

Forming or containing small cavities within a cell

Monotherapy

A medicine taken by itself (one type of treatment)

Movement disorders

A range of conditions characterised by abnormal body movements

Magnetic Resonance Imaging

MRI; a machine that shows the internal structure of the body on a screen

Myelin sheath

A protein cover found around some nerve fibres in the body that helps rapid transmission of nerve impulses

Neuropathology

The study of diseases occurring in the brain or nervous system

Oedema

Accumulation of fluid in body tissues from injury, inflammation or disease, resulting in swelling

Opisthotonus

A bodily position where the head, neck and spine are arched backwards

Optic tract

Part of the visual system in the brain

Paediatric

Occurring in children

Partial epilepsy

A **seizure** that affects only one part of the brain

Pathology

The study of diseases

Prevalence

A measure of disease rates, based on the current number of cases in a particular population at a particular time, or over a particular period

Relative risk

A measure of risk for one group compared with another, usually accompanied by a 95% confidence interval (CI), which indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the relative risk is statistically significant.

Reticular formation

An area at the rear of the brain involved in the sleep cycle

Retrospective cohort comparative epidemiological study

A study in which past medical records of groups of individuals who are alike except for one particular characteristic are compared for an outcome, to study the occurrence, distribution or control of diseases in populations.

Risk factor

A substance or activity that increases the likelihood of an individual developing an illness or medical condition

Seizure

Uncontrolled electrical activity in the brain that produces fits or convulsions of the body

Spasticity

Constant and unwanted contraction of muscle groups resulting from damage to the brain or spinal cord

Steroids

A group of chemical substances found naturally in the body (eg, hormones) or taken as medicines (anti-inflammatories)

T2 weighted signal

A type of image produced by an MRI scan

Tardive dyskinesia

Involuntary repeated movements of the face, tongue and limbs

Thalamus

A part of the brain that processes body sensations and regulates consciousness and sleep

Tibutation

A tremor of the head

Transient

Temporary

Vasogenic oedema

Swelling of, or around, blood vessels

White matter

One of two types of nerve tissue in the central nervous system that consists mainly of **myelinated** nerve fibres