IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0827/003/001
Case No: 2082959

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Cephalon UK Limited

1 Albany Place, **Hyde Way, Welwyn Garden City**, **Hertfordshire**, **AL7 3BT**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Gabitril 2.5 mg, film-coated tablet

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/05/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gabitril 2.5 mg, film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Gabitril 2.5 mg tablet contains:
Tiagabine 2.5 mg (as hydrochloride monohydrate)

Excipients:
Each Gabitril 2.5 mg film-coated tablet contains 29 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gabitril 2.5 mg film-coated tablet is a white, round biconvex film-coated tablet embossed on one side with "254".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Add-on treatment of partial seizures with or without secondary generalisation which are not satisfactorily controlled with other anti-epileptic drugs.

The drug should only be used in adults and adolescents over 12 years.

4.2 Posology and method of administration

Gabitril is given orally and should be taken with meals.

Dosing schemes may need to be individualised based upon a patient’s particular characteristics such as age, liver function and concomitant medications (see section 4.5).

The initial daily dose should be taken as a single dose or divided into two doses. The daily maintenance dose should be divided into two or three single doses.

Tiagabine is not recommended for use in children below 12 years due to a lack of data on safety and efficacy. (See section 4.4).

<u>Adults and adolescents over 12 years</u>:

<u>In association with enzyme-inducing drugs:</u>
The initial daily dose is 5-10 mg tiagabine, followed by weekly increments of 5-10 mg/day. The usual maintenance dose in patients taking enzyme-inducing drugs is 30-50 mg/day. Doses up to 70 mg/day are well tolerated.

<u>In association with non enzyme-inducing drugs:</u>
The initial daily dose is 5-10 mg tiagabine, followed by weekly increments of 5-10 mg/day.
The usual maintenance dose in patients taking non enzyme-inducing drugs is 15-30 mg/day.

Elderly: The pharmacokinetic properties of tiagabine do not seem to be significantly modified in the elderly. However, only limited information is available on the use of Gabitril in elderly patients. It is therefore recommended to use tiagabine with caution in this age group.

Patients with renal insufficiency: Renal insufficiency does not affect the pharmacokinetics of tiagabine, therefore the dosage does not need to be modified in this type of patient.

Patients with impaired liver function: Tiagabine is metabolised in the liver and since the pharmacokinetics of tiagabine in patients with mild to moderate impaired liver function is modified (see Section 5.2), the Gabitril dosage should be adjusted by reducing the individual doses and/or prolonging the dose intervals.

4.3 Contraindications

Gabitril should not be used in case of:
- Hypersensitivity to tiagabine or to any of the excipients.
- Severely impaired liver function.

4.4 Special warnings and precautions for use

In the absence of clinical data, Gabitril is generally not to be recommended in generalised epilepsy, particularly the idiopathic forms with absences and Lennox Gastaut syndrome, or similar forms. Furthermore, in view of the GABAergic mode of action of tiagabine and the data from animal studies, a risk of aggravation of absences in patients with generalised epilepsy treated with Gabitril cannot be excluded.
Tiagabine is not recommended for use in children below 12 years due to a lack of data on safety and efficacy. (See section 4.2).

Post-marketing reports have shown that Gabitril use has been associated with new onset seizures and status epilepticus in patients without epilepsy. Although seizures have been reported in patients taking normal daily doses of tiagabine, most of the cases have been reported in context of overdoses (see section 4.9) or after a too fast titration rate. Other confounding factors that may have contributed to development of seizures in non epileptic patients include underlying medical conditions or concomitant medications that can reduce seizure threshold.
Safety and effectiveness of Gabitril have not been established for any indication other than add-on treatment of partial seizures with or without secondary generalization in adults and adolescents over 12 years not satisfactory controlled with other anti-epileptic drugs.

As with all other anti-epileptic drugs, abrupt discontinuation of the treatment may cause recurrence of seizures. It is therefore recommended to reduce the dose gradually over a period of 2-3 weeks.

In patients with a history of serious behavioural problems including generalised anxiety and depression, there is a risk of recurrence of these symptoms during treatment with Gabitril, as can be seen with certain other anti-epileptic drugs. Treatment should therefore be started with a low initial dose under careful clinical observation.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for tiagabine.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

As with other anti-epileptic drugs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with tiagabine. These phenomena may be the consequence of an overdose, a decrease in plasma concentrations of concomitantly used anti-epileptics, progress of the disease, or a paradoxical effect.

Spontaneous ecchymoses have been reported. Therefore, if ecchymoses are observed, full blood count including platelet count should be performed.

Rare cases of visual field defects have been reported with tiagabine. If visual symptoms develop, the patient should be referred to an ophthalmologist for further evaluation including perimetry.

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with drugs involving CYP 3A4/5 metabolism:

Anti-epileptic agents which induce hepatic enzymes (CYP 450) such as phenytoin, carbamazepine, phenobarbital, and primidone enhance the metabolism of tiagabine.

Rifampicine (CYP inducer) enhances the metabolism of tiagabine.

In case of combination with one or several of these drugs (anti-epileptic agents, rifampicine), the dose of tiagabine could be adapted: increase of daily dose and/or more frequent administration in order to achieve the clinical response.

Concomitant use with non-inducing drugs:

Following a given dose of tiagabine, the estimated plasma concentration in non-induced patients is more than twice that in patients receiving enzyme-inducing agents. To achieve similar systemic exposures of tiagabine, non-induced patients require lower and less frequent doses of tiagabine than induced patients. These patients may also require a slower titration of tiagabine compared to that of induced patients.

Gabitril does not have any clinically significant effect on the plasma concentrations of phenytoin, carbamazepine, phenobarbital, valproate, warfarin, digoxin, theophylline and hormones from oral contraceptives.

Cimetidine does not have a clinically significant effect on tiagabine plasma levels.

4.6 Pregnancy and lactation

Animal experiments have not shown a teratogenic effect of tiagabine.
Studies in animals have, however, revealed peri- and post-natal toxicity of tiagabine in very high doses.

Clinical experience of the use of Gabitril in pregnant women is limited.
No information on Gabitril during breast-feeding is available.

Consequently, as a precautionary measure, it is preferable not to use Gabitril during pregnancy or breast-feeding.

4.7 Effects on ability to drive and use machines

Gabitril might cause dizziness or other CNS related symptoms, especially during initial treatment. Therefore, caution should be shown by patients driving vehicles or operating machinery.

4.8 Undesirable effects

Adverse events are generally mild to moderate. Most events occur during the titration phase and are often transient.

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10 000 < 1/1,000), unknown (cannot be estimated from the available data).

Psychiatric disorders
Very common: Depressed mood, Nervousness, Mental concentration difficulty
Common: Emotional lability.
Rare: Confusion, Paranoïd reactions (hallucination, agitation and delusion).

Nervous system disorders
Very common: Dizziness, Tremor, Somnolence
Rare: Non-convulsive status epilepticus,
Unknown: Encephalopathy

Eye disorders
Rare: Visual field defects (see section 4.4)

Gastro-intestinal system disorders
Common: Diarrhoea

Skin and subcutaneous tissue disorders
Common: Ecchymoses

General disorders and administration site conditions
Very common: Tiredness

Investigations
Rare: Slow-down EEG associated with a rapid titration phase or tiagabine increasing dose

Post marketing:
Post-marketing reports have shown that Gabitril use has been associated with new onset seizures and status epilepticus in patients without epilepsy treated by tiagabine for unapproved indication (see section 4.4).

4.9 Overdose

Symptoms most often accompanying Gabitril overdose, alone or in combination with other drugs, have included seizures, including status epilepticus, in patients with and without underlying seizure disorders, mute and withdrawn appearance of the patient, coma, ataxia or incoordination, somnolence, dizziness, confusion, impaired speech, agitation, myoclonus, spike wave stupor, tremors, vomiting and hostility. Respiratory depression has been seen in the context of seizures.

From post-marketing experience, there have been no reports of fatal overdoses involving Gabitril alone (doses up to 720 mg), although a number of patients required intubation and ventilatory support as part of the management of their status epilepticus.

In case of overdose, standard symptomatic treatment is recommended. Hospitalisation can be recommended in case of severe overdoses.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptic / fatty acid derivative
ATC code: N03A G06

Tiagabine is a potent and selective inhibitor of both neuronal and glial GABA uptake.
Treatment with Gabitril leads to an increase in brain levels of GABA, the major inhibitory neurotransmitter in the brain.

Tiagabine lacks significant affinity for other neurotransmitter receptor binding and/or uptake sites.

5.2 Pharmacokinetic properties

Absorption
Tiagabine is rapidly and virtually completely absorbed from the gastro-intestinal tract, with an absolute bioavailability of 89%. Administration of Gabitril with food results in a lower plasma concentration peak and a delay of the peak, but without changing the total quantity absorbed.

Distribution
The volume of distribution is approximately 1 l/kg. Plasma protein binding of tiagabine is about 96%.

Biotransformation / Elimination
Tiagabine is widely metabolised in humans, mainly by the liver CYP3A system.
There is no evidence that tiagabine causes induction or inhibition of cytochrome P450. Conversely, other antiepileptics such as phenytoin, carbamazepine, phenobarbital, and primidone increase the hepatic clearance of tiagabine when given concomitantly.

The plasma half-life of tiagabine which is normally 7-9 hours, is reduced to 2-3 hours in combination with these substances.
In the urine less than 1% is excreted unchanged and 14% as two 5-oxo-thiolene isomers. The rest is excreted in faeces as metabolites. No active metabolites have been identified.

Hepatic insufficiency
A study in patients with mild to moderate impaired liver function has shown a 50% increase of the plasma concentration peak of tiagabine and a 70% increase of the area under the curve. The half-life of tiagabine is prolonged with the degree of impairment of liver function. However, no patients with severe impairment of liver function were included in the study (see section 4.3).

The dosage of tiagabine should be modified in patients with mild to moderate impaired liver function (see section 4.2).

5.3 Preclinical safety data

A long term carcinogenicity study in rats revealed a slightly increased incidence of hepatocellular adenomas in females in the high dose (200 mg/kg). The drug is non-genotoxic. The clinical relevance of these abnormalities is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline (E460)
Ascorbic acid (E300)
Lactose anhydrous
Starch, pregelatinised (maize)
Crospovidone
Silica, colloidal anhydrous (E 551)
Hydrogenated vegetable oil (Type 1)
Stearic acid
Magnesium stearate

Film-coating:
Hypromellose
Hydroxypropylcellulose (E463)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Store in the original package.

6.5 Nature and contents of container

Child resistant, white polyethylene bottles with white polypropylene screw closures. Each bottle contains a high density polyethylene canister of activated clay desiccant**.**
Packs containing 20, 30, 50, 100 (2 bottles of 50) and 200 (4 bottles of 50) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cephalon UK Ltd.
1 Albany Place
Hyde Way
Welwyn Garden City
Hertfordshire AL7 3BT
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0827/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2002
Date of last renewal: 14 June 2006

10 DATE OF REVISION OF THE TEXT

January 2009