Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gabitril 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Gabitril 10 mg tablet contains:
Tiagabine 10 mg (as hydrochloride monohydrate)

Excipient(s) with know effect:
Each Gabitril 10 mg film-coated tablet contains 117 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gabitril 10 mg film-coated tablet is a white, oval biconvex film-coated tablet embossed on one side with "252".

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 medicinal products.

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

4.2 Posology and method of administration

Posology
Rapid titration and/or large dose increments of tiagabine may not be well-tolerated and should be avoided (see section 4.4)
Paediatric population below 12 years
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).

Adults and adolescents over 12 years:
Dosing schemes may need to be individualised based upon a patient's particular characteristics such as age, liver function and concomitant medicinal products (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.

In association with enzyme-inducing medicinal products:
The initial dose is 5-10 mg/day tiagabine, followed by dose titration in weekly increments of 5-10 mg/day to reach the maintenance dose.
The usual maintenance dose in patients taking enzyme-inducing medicinal products is 30-50 mg/day. Doses up to 70 mg/day are well tolerated.

In association with non enzyme-inducing medicinal products:
The initial dose is 5-10 mg/day tiagabine, followed by dose titration in weekly increments of 5-10 mg/day to reach the maintenance dose.

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.

Method of administration
Gabitril is given orally and should be taken with meals.

4.3 Contraindications

Gabitril should not be used in case of:
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Severely impaired liver function.
- combination with St John Wort (Hypericum perforatum) (see section 4.5).

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 medicinal products that can reduce seizure threshold.

Rapid titration and/or large dose increments of tiagabine may not be well-tolerated and should be avoided (see section 4.2).

As with all other anti-epileptic medicinal products, 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 medicinal products. 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 medicinal products 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 medicinal products, 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.

Paediatric population
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 medicinal products.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use with medicinal products 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.
The combination of tiagabine with St John Wort (Hypericum perforatum) may lead to lower exposure and loss of efficacy of tiagabine, due to the potent induction of CYP3A4 by St John Wort (increasing tiagabine metabolism). Therefore, the combination of tiagabine with St John's Wort is contra-indicated (see also section 4.3).

Rifampicine (CYP inducer) enhances the metabolism of tiagabine.

In case of combination with one or several of these medicinal products (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 medicinal products:
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 Fertility, 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.

Pregnancy
Clinical experience of the use of Gabitril in pregnant women is limited.

Breastfeeding
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.

Fertility
No data on fertility are available.

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 (see section 4.2).

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), not known (cannot be estimated from the available data).

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

Nervous system disorders
Very common: Dizziness, Tremor, Somnolence
Rare: Non-convulsive status epilepticus
Not known: Encephalopathy, amnesia

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

Gastrointestinal disorders
Very common: Nausea
Common: Diarrhoea, Abdominal pain

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 data:
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).
During post-marketing experience, there have been reports of vision blurred, vomiting, ataxia, abnormal gait, speech disorder, hostility, insomnia, dermatitis bullous, vesiculobullous rash,muscle twitching and amnesia. In case reports, amnesia occurred within days after initiation or dose increase of tiagabine and was reversible upon discontinuation of tiagabine or dose decrease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms most often accompanying Gabitril overdose, alone or in combination with other medicinal products, have included seizures, including status epilepticus, in patients with and without underlying seizure disorders, mute and withdrawn appearance of the patient, amnesia, coma, spike wave stupor, encephalopathy, somnolence, dyskinesia, myoclonus, tremors, ataxia or incoordination, dizziness, impaired speech, hostility, agitation, vomiting, and 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-epileptics, fatty acid derivatives, ATC code: N03AG06

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

4 years

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package.

6.5 Nature and contents of container

Child resistant, white polyethylene bottles with white polypropylene screw closures with an embedded desiccant agent. Packs containing 20, 30, 50, 100 and 200 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/199/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 March 1997
Date of last renewal: 14 June 2006

10 DATE OF REVISION OF THE TEXT

June 2022