Gabitril 10 mg Film-coated Tablets

Summary of Product Characteristics Updated 09-Mar-2023 | Cephalon (UK) Limited

1. Name of the medicinal product

Gabitril® 10 mg film-coated tablets

2. Qualitative and quantitative composition

Each Gabitril 10 mg tablet contains:

Tiagabine anhydrous, INN 10 mg (as hydrochloride monohydrate)

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

10 mg: Tablet. White, oval biconvex film-coated tablet embossed on one side with '252'.

4. Clinical particulars

4.1 Therapeutic indications

Gabitril is an anti-epileptic drug indicated as add-on therapy for partial seizures with or without secondary generalisation where control is not achieved by optimal doses of at least one other anti-epileptic drug.

4.2 Posology and method of administration

Gabitril should be taken orally with meals.

Dosing schemes may need to be individualised based upon a patient's particular characteristics such as age and concomitant medications.

Concomitant use with drugs involving CYP 3A4/5 metabolism: As CYP3A4/5 is involved in the metabolism of tiagabine, it is recommended that the dose of tiagabine is adjusted when it is taken in combination with CYP3A4/5 inducers (see section 4.5 Interactions with other medicinal products and other forms of interactions).

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. Dosage adjustment of tiagabine should be considered whenever a change in patient's metabolic enzyme-inducing status occurs as a result of the addition, discontinuation, or dose change of the enzyme-inducing agent.

Adults and children over 12 years: 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 30-45 mg/day. In patients not taking enzyme-inducing drugs, the maintenance dose should initially be reduced to 15-30 mg/day. 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.

Children under 12 years: There is no experience with Gabitril in children under 12 years of age and as such Gabitril should not be used in this age group.

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 tiagabine 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 these types of patients.

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.

Gabitril should not be used in patients with severely impaired hepatic function (see Section 4.3).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Severely impaired liver function.

Gabitril in combination with St John's Wort (Hypericum perforatum) (see section 4.5).

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic 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 Gabitril.

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.

Post-marketing reports have shown that Gabitril use has been associated with new onset seizures and status epilepticus in patients without epilepsy. Confounding factors that may have contributed to development of seizures include underlying medical conditions or concomitant medications that can reduce seizure threshold, reported overdose and manner of dose administration (e.g. high dosage, fast titration rate).

Safety and effectiveness of Gabitril have not been established for any indication other than as adjunctive therapy for partial seizures in adults and adolescents over 12 years.

Gabitril is eliminated by hepatic metabolism and therefore caution should be exercised when administering the product to patients with impaired hepatic function. Reduced doses and/or dose intervals should be used and patients should be monitored closely for adverse events such as dizziness and tiredness.

Although Gabitril may slightly prolong the CNS depressant effect of triazolam, this interaction is unlikely to be relevant to clinical practice.

Anti-epileptic agents that induce hepatic enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of tiagabine. Consequently, patients taking enzyme-inducing drugs may require doses of tiagabine above the usual dose range.

Although there is no evidence of withdrawal seizures following Gabitril, it is recommended to taper off treatment over a period of 2-3 weeks.

Serious rash, including vesiculobullous rash, has occured in patients receiving Gabitril (see section 4.8 Undesirable effects).

Spontaneous bruising has been reported. Therefore, if bruising is observed full blood count, including platelet count is to 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.

Gabitril tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

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

4.5 Interaction with other medicinal products and other forms of interaction

Anti-epileptic agents that induce hepatic enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of tiagabine. The plasma concentration of tiagabine may be reduced by a factor 1.5-3 by concomitant use of these drugs.

Gabitril does not have any clinically significant effect on the plasma concentrations of phenytoin, carbamazepine, phenobarbital, warfarin, digoxin, theophylline and hormones from oral contraceptive pills. Gabitril reduces the plasma concentration of valproate by about 10%, and cimetidine increases the bioavailability of tiagabine by about 5%. Neither of these findings are considered clinically important and do not warrant a dose modification.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breast-feeding

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 unless in the opinion of the physician, the potential benefits of treatment outweigh the potential risks.

4.7 Effects on ability to drive and use machines

Gabitril may 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 mainly CNS related.

A full list of adverse reactions reported with Gabitril during clinical studies and post marketing experience is shown in the table below. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data):

The following undesirable effects have been reported with Gabitril:

System Organ Class	Frequency	Undesirable effects
Psychiatric disorders	Very common	Nervousness (non-specific)
	Common	Concentration difficulties, depressed mood, emotional lability, confusion, insomnia, hostility/aggression
	Uncommon	Depression, psychosis
	Rare	Hallucinations, delusion
Nervous system disorders	Very common	Dizziness, tremor
	Common	Ataxia, abnormal gait, speech disorder
	Uncommon	Somnolence
	Rare	Non-convulsive status epilepticus
	Not known	Encephalopathy, amnesia
Eye disorders	Common	Vision blurred
	Rare	Visual field defects
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis bullous, bruising
	Not known	Vesiculobullous rash, exfoliative dermatitis
Musculoskeletal and connective tissue disorders	Common	Muscle twitching
General disorders and administration site conditions	Very common	Tiredness
Injury, poisoning and procedural complications	Common	Accidental injury

In patients with a history of serious behavioural problems there is a risk of recurrence of these symptoms during treatment with Gabitril, as occurs with certain other anti-epileptic drugs.

Although not statistically significant, routine laboratory screening during placebo controlled studies showed a low white blood cell count (<2.5 x 10^9 per litre) more frequently during Gabitril treatment (4.1%) than placebo (1.5%).

Postmarketing 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 Special warnings and special precautions for use).

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 authorization 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, respiratory depression, respiratory arrest, coma, loss of consciousness, spike wave stupor, encephalopathy, amnesia, confusion, disorientation, somnolence, dyskinesia, myoclonus, tremors, ataxia or incoordination, dizziness, nystagmus, impaired speech, headache, psychotic disorder, hallucinations, hostility, aggression, agitation, vomiting, hypersalivation, bradycardia, tachycardia, ST wave changes, hypertension, hypotension and urinary incontinence. In more severe instances, mute and withdrawn appearance of the patient and risk of convulsion have been reported.

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 and medical observation with supportive care is recommended. Hospitalisation can be recommended in cases of severe overdoses. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of more than 2 mg/kg.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Gabitril is an anti-epileptic drug.

Tiagabine is a potent and selective inhibitor of both neuronal and glial GABA uptake, which results in an increase in GABAergic medicated inhibition in the brain.

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

5.2 Pharmacokinetic properties

Tiagabine is rapidly and virtually completely absorbed from Gabitril tablets, with an absolute bioavailability of 89%. Administration with food results in a decreased rate and not extent of absorption.

The volume of distribution is approximately 1 L/kg.

Plasma protein binding of tiagabine is about 96%.

Renal clearance is negligible. Hepatic metabolism is the principle route for elimination of tiagabine. Less than 2% of the dose is excreted unchanged in urine and faeces. No active metabolites have been identified. Other anti-epileptic drugs such as phenytoin, carbamazepine, phenobarbital and primidone induce hepatic drug metabolism and the hepatic clearance of tiagabine is increased when given concomitantly with these drugs.

There is no evidence that tiagabine causes clinically significant induction or inhibition of hepatic drug metabolising enzymes at clinical doses.

The plasma elimination half-life of tiagabine is 7–9 hours, except in induced patients where it is 2-3 hours.

Absorption and elimination of tiagabine are linear within the therapeutic dose range.

Hepatic insufficiency

A study in patients with mild and moderate impaired liver function has shown a 50% increase of the plasma concentration peak (Cmax) and a 70% increase of the area under the curve (AUC) for total (free plus bound) tiagabine in impaired individuals as compared to individuals with normal hepatic function. The fraction of unbound drug was greater in patients with moderate hepatic impairment and, as a result, exposure to unbound drug was increased to a greater extent (up to 2-fold) in moderately impaired individuals as compared to individuals with normal hepatic function. Tiagabine half-life ($T_{1/2}$) is prolonged in patients with impaired liver function with the extent of prolongation increasing with increased level of hepatic impairment. Due to adverse events observed in the patients with moderate impairment, patients with severe hepatic impairment were not studied (see Section 4.3).

The dosage of tiagabine should be carefully titrated in patients with epilepsy and reduced hepatic function. Lower doses or longer dosing intervals may be required in patients with mild to moderate impairment in liver function (see Section 4.2).

5.3 Preclinical safety data

Animal safety data carried out in the rat, mouse and dog gave no clear evidence of specific organ toxicity nor any findings of concern for the therapeutic use of tiagabine. The dog appears to be particularly sensitive to the pharmacological actions of tiagabine and clinical signs such as sedation, insensibility, ataxia and visual impairment reflecting CNS effects were seen at daily doses of 0.5 mg/kg and above in a dose related manner. The results of a wide range of mutagenicity tests showed that tiagabine is unlikely to be genotoxic to humans. Clastogenic activity was seen only at cytotoxic concentrations (>>200-fold human plasma levels) using the *in-vitro* human lymphocyte test in the absence of a metabolising system. In long-term carcinogenicity studies conducted in the rat and mouse, only the rat study revealed slightly increased incidences of hepatocellular adenomas in females and benign Leydig cell tumours in the high dose (200 mg/kg/day) group only. These changes are considered to be rat-specific and macrophages and inflammation were seen at a higher incidence than normal. The significance of this latter finding is unknown.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet Core:

Cellulose, microcrystalline (E460)

Ascorbic acid (E300)

Lactose

Starch, pregelatinised (maize)

Crospovidone

Silica, colloidal anhydrous (E551)

Hydrogenated vegetable oil (Type 1)

Stearic acid

Magnesium stearate

Film-coating:

Opadry White 20A280023

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Hypromellose

Hydroxypropylcellulose (E463)

Titanium Dioxide (E171)

6.2 Incompatibilities

None.

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 50 and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Cephalon UK Limited

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8. Marketing authorisation number(s)

PL 16260/0010

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 30th September 2002

Date of latest renewal: 31th August 2006

10. Date of revision of the text

22/02/2023

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