SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gabitril® 5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Gabitril 5 mg tablet contains:
Tiagabine anhydrous, INN 5 mg (as hydrochloride monohydrate)

Excipient(s) with known effect:
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

5 mg: Tablet. White, round biconvex film-coated tablet embossed on one side with ‘251’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Gabitril is an antiepileptic 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 antiepileptic 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.

*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:* There is limited information available on the use of Gabitril in elderly patients, but pharmacokinetics of tiagabine are unchanged, hence there should be no need for dose modification.

*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 occurred 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 \( \geq 1/10 \), common \( \geq 1/100 \text{ to } <1/10 \), uncommon \( \geq 1/1,000 \text{ to } <1/100 \), rare \( \geq 1/10,000 \text{ to } <1/1,000 \); very rare \( <1/10,000 \), not known (cannot be estimated from the available data):

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

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 10⁹ 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 (see section 4.4 Special warnings and special precautions for use).

**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
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.

Standard medical observation and supportive care should be given. 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 antiepileptic drug.

Tiagabine is a potent and selective inhibitor of both neuronal and glial GABA uptake, which results in an increase in GABAergic mediated 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 (T1/2) 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 as clinical signs such as sedation, insensibility, ataxia and visual impairment reflecting CNS effects were seen at daily doses of 0.5mg/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) in 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 (200mg/kg/day) group only. These changes are considered to be ratspecific and of little clinical importance to humans. In rats treated with 100mg/kg/day or more, pulmonary 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, anhydrous
- Starch, pregelatinised (maize)
- Crospovidone
- Silica, colloidal anhydrous (E551)
- Hydrogenated vegetable oil (Type 1)
- Stearic acid
- Magnesium stearate

*Film-coating:*
- Hypromellose
- Hydroxypropylcellulose (E463)
- Titanium Dioxide (E171)

6.2 **Incompatibilities**

None.

6.3 **Shelf life**

3 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.

6.6 **Special precautions for disposal**
No special instructions.

7 MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
Ridings Point
Whistler Drive
Castleford
West Yorkshire
WF10 5HX
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16260/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/08/2006

10 DATE OF REVISION OF THE TEXT

08/07/2016