

## **Public Assessment Report**

### **Decentralised Procedure**

**Gabapentin 100 mg capsules, hard**  
**Gabapentin 300 mg capsules, hard**  
**Gabapentin 400 mg capsules, hard**

**PL 20532/0114**  
**PL 20532/0115**  
**PL 20532/0116**

**UK/H/1165/01/DC**  
**UK/H/1165/02/DC**  
**UK/H/1165/03/DC**

**Aurobindo Pharma Limited**

## **Lay summary**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products Gabapentin 100 mg, 300 mg and 400 mg capsules, hard (product licence numbers: PL 20532/0114-6) on 23 December 2010. These medicines are available on prescription only.

Gabapentin belongs to a group of medicines used to treat epilepsy and peripheral neuropathic pain (long lasting pain caused by damage to the nerves). Gabapentin is used to treat:

- Various forms of epilepsy (seizures that are initially limited to certain parts of the brain, whether the seizure spreads to other parts of the brain or not): gabapentin may be used to treat epilepsy in patients whose current treatment is not fully controlling their condition. In these cases gabapentin is usually taken in addition to the current treatment. Gabapentin can also be used on its own to treat adults and children over 12 years of age.
- Peripheral neuropathic pain: a variety of different disease can cause peripheral neuropathic pain (primarily occurring in the legs and/or arms), such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles, etc.

The data submitted in support of these applications for Gabapentin 100 mg, 300 mg and 400 mg capsules raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

## TABLE OF CONTENTS

Module 1: Information about Decentralised Procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflet	Page 44
Module 4: Labelling	Page 48
Module 5: Scientific Discussion	Page 54
1 Introduction	
2 Quality aspects	
3 Preclinical aspects	
4 Clinical aspects	
5 Overall conclusions	

## Module 1

### Information about Decentralised Procedure

Name of the product in the Reference Member State	Gabapentin 100 mg, 300 mg and 400 mg capsules, hard
Type of application	Generic (Article 10.1)
Name of the active substance (INN)	Gabapentin
Pharmacotherapeutic classification (ATC code)	Other antiepileptics (N03AX12)
Pharmaceutical form and strength	Capsule, hard; 100, 300 and 400 mg
Reference number for the Decentralised Procedure	UK/H/1165/01-03/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, BG, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK
Start of Decentralised Procedure	24 September 2007
End date of Decentralised Procedure	25 November 2010
Marketing Authorisation number	PL 20532/0114-6
Name and address of the authorisation holder	Aurobindo Pharma Limited Ares, Odyssey Business Park, West End Road South Ruislip HA4 6QD United Kingdom

## Module 2

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Gabapentin 100 mg capsules, hard

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg hard capsule contains 100 mg gabapentin.

For a full list of excipients, see section 6.1

#### 3 PHARMACEUTICAL FORM

Capsule, hard

Gabapentin 100 mg capsules, hard, imprinted with 'D' on white cap and '02' on white body, containing white to off-white crystalline powder.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

###### Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above (see section 5.1).

Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

###### Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

##### 4.2 Posology and method of administration

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1:

Dosing Chart – Initial Titration

Day 1 – 300 mg once a day  
Day 2 – 300 mg two times a day  
Day 3 - 300 mg three times a day

#### Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

#### **Epilepsy**

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.

#### *Adults and adolescents:*

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

#### *Children aged 6 years and above:*

The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

#### **Peripheral neuropathic pain**

##### *Adults*

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

#### **Instruction for all areas of indication**

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

#### Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

#### **Use in patients with renal impairment**

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

<b>Table 2</b>	
<b>Dosage of Gabapentin in adults based on renal function</b>	
<b>Creatinine Clearance (ml/min)</b>	<b>Total daily dose<sup>a</sup> (mg/day)</b>
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 <sup>b</sup> -600
< 15 <sup>c</sup>	150 <sup>b</sup> -300

<sup>a</sup> Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).

<sup>b</sup> To be administered as 300 mg every other day.

<sup>c</sup> For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

#### **Use in patients undergoing haemodialysis**

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

### 4.3 **Contraindications**

Hypersensitivity to gabapentin or to any of the excipients.

### 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 gabapentin

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

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

#### **Laboratory tests**

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify

such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Notice: The HDPE bottle contains desiccant. Do not swallow.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these anti-epileptic agents.

Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Coadministration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

#### **4.6 Pregnancy and lactation**

##### **Risk related to epilepsy and antiepileptic medicinal products in general**

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

### **Risk related to gabapentin**

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

#### **4.7 Effects on ability to drive and use machines**

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

#### **4.8 Undesirable effects**

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency [very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ )]. Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

##### *Infections and infestations*

Very Common: Viral infection

Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

##### *Blood and the lymphatic system disorders*

Common: leucopenia

Not known: thrombocytopenia

##### *Immune system disorders*

Uncommon: allergic reactions (e.g. urticaria)

Not known: hypersensitivity syndrome, a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms

Metabolism and Nutrition Disorders

Common: anorexia, increased appetite

Psychiatric disorders

Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal

Not known: hallucinations

Nervous system disorders

Very Common: somnolence, dizziness, ataxia,

Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes

Uncommon: hypokinesia

Not known: other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders

Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders

Common: vertigo

Not known: tinnitus

Cardiac disorders

Uncommon: palpitations

Vascular disorder

Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders

Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence

Not known: pancreatitis

Hepatobiliary disorders

Not known: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne

Not known: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia, myalgia, back pain, twitching

Not known: myoclonus

Renal and urinary disorders

Not known: acute renal failure, incontinence

Reproductive system and breast disorders

Common: impotence

Not known: breast hypertrophy, gynaecomastia

General disorders and administration site conditions

Very Common: fatigue, fever  
Common: peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome  
Uncommon: generalized oedema  
Not known: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

#### Investigations

Common: WBC (white blood cell count) decreased, weight gain  
Uncommon: elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin  
Not known: blood glucose fluctuations in patients with diabetes

#### Injury and poisoning

Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

## **4.9 Overdose**

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is not usually required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other Antiepileptics

ATC code: N03AX12

The precise mechanism of action of gabapentin is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives.

The binding site for gabapentin has been identified as the  $\alpha_2$ -delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including GABA<sub>A</sub>, GABA<sub>B</sub>, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100  $\mu$ M, which are not achieved *in vivo*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*.

Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years).

The data from this additional post-hoc analysis are summarised in the table below:

Response ( $\geq$ 50% improved) by treatment and age MITT* Population			
Age category	Placebo	Gabapentin	P-value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

\*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

## 5.2 Pharmacokinetic properties

### Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%.

Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 µg/ml and 20 µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N = 14)	
	Mean	% CV	Mean	% CV	Mean	% CV
C <sub>max</sub> (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
T <sub>max</sub> (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T <sub>1/2</sub> (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC <sub>0-t</sub> (µg.hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

C<sub>max</sub> = Maximum steady state plasma concentration

t<sub>max</sub> = Time for C<sub>max</sub>

T<sub>1/2</sub> = Elimination half-life

AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose

Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose

NA = Not available

### Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

### Metabolism

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

### Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

#### Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

### **5.3 Preclinical safety data**

#### Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

#### Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

#### Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m<sup>2</sup> of body surface area basis).

#### Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m<sup>2</sup> basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m<sup>2</sup> basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m<sup>2</sup> basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m<sup>2</sup> basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m<sup>2</sup> basis.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule Fill:

Maize starch

Talc

#### Capsule Shell:

Titanium dioxide (E171)

Sodium lauril sulfate

gelatin

#### **Printing ink**

Shellac

Propylene glycol

Black iron oxide

Potassium hydroxide

### **6.2 Incompatibilities**

Not applicable.

- 6.3 Shelf life**  
2 years.  
In use shelf life for HDPE bottle pack: 30 days
- 6.4 Special precautions for storage**  
Store below 25<sup>0</sup>C.  
Blister pack: Store in the original package.  
HDPE bottle pack: Store in the original container.
- 6.5 Nature and contents of container**  
Blister pack of Polyamide/Aluminium /PVC and Aluminium foil:  
10, 20, 30, 50, 60, 90, 100 and 200 capsules, hard.  
  
HDPE bottle with polypropylene cap containing silica gel desiccant:  
100, 200 and 1000 capsules, hard.  
Not all pack sizes may be marketed
- 6.6 Special precautions for disposal**  
No special requirements.
- 7 MARKETING AUTHORISATION HOLDER**  
Aurobindo Pharma Limited  
Ares, Odyssey Business Park, West End Road  
South Ruislip HA4 6QD  
United Kingdom
- 8 MARKETING AUTHORISATION NUMBER(S)**  
PL 20532/0114
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
23/12/2010
- 10 DATE OF REVISION OF THE TEXT**  
23/12/2010

**1 NAME OF THE MEDICINAL PRODUCT**

Gabapentin 300 mg capsules, hard

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 300 mg hard capsule contains 300 mg gabapentin.

For a full list of excipients, see section 6.1

**3 PHARMACEUTICAL FORM**

Capsule, hard

Gabapentin 300 mg capsules, hard, imprinted with 'D' on yellow cap and '03' on yellow body, containing white to off-white crystalline powder.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above (see section 5.1).

Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

**4.2 Posology and method of administration**

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1:

Dosing Chart – Initial Titration

Day 1 – 300 mg once a day

Day 2 – 300 mg two times a day

Day 3 - 300 mg three times a day

Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

### **Epilepsy**

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.

#### *Adults and adolescents:*

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

#### *Children aged 6 years and above:*

The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

### **Peripheral neuropathic pain**

#### *Adults*

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral

neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

#### **Instruction for all areas of indication**

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

#### Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

#### **Use in patients with renal impairment**

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

<b>Table 2</b>	
<b>Dosage of Gabapentin in adults based on renal function</b>	
<b>Creatinine Clearance (ml/min)</b>	<b>Total daily dose<sup>a</sup> (mg/day)</b>
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 <sup>b</sup> -600
< 15 <sup>c</sup>	150 <sup>b</sup> -300

<sup>a</sup> Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).

<sup>b</sup> To be administered as 300 mg every other day.

<sup>c</sup> For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

#### **Use in patients undergoing haemodialysis**

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

### **4.3 Contraindications**

Hypersensitivity to gabapentin or to any of the excipients.

#### **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 gabapentin

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

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

##### **Laboratory tests**

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Notice: The HDPE bottle contains desiccant. Do not swallow.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these anti-epileptic agents.

Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Coadministration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

#### **4.6 Pregnancy and lactation**

##### **Risk related to epilepsy and antiepileptic medicinal products in general**

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

##### **Risk related to gabapentin**

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

#### **4.7 Effects on ability to drive and use machines**

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

#### **4.8 Undesirable effects**

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency [very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ )]. Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

##### *Infections and infestations*

Very Common: Viral infection

Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

##### *Blood and the lymphatic system disorders*

Common: leucopenia

Not known: thrombocytopenia

##### *Immune system disorders*

Uncommon: allergic reactions (e.g. urticaria)

Not known: hypersensitivity syndrome, a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms

Metabolism and Nutrition Disorders

Common: anorexia, increased appetite

Psychiatric disorders

Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal

Not known: hallucinations

Nervous system disorders

Very Common: somnolence, dizziness, ataxia,

Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes

Uncommon: hypokinesia

Not known: other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders

Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders

Common: vertigo

Not known: tinnitus

Cardiac disorders

Uncommon: palpitations

Vascular disorder

Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders

Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence

Not known: pancreatitis

Hepatobiliary disorders

Not known: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne

Not known: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia, myalgia, back pain, twitching

Not known: myoclonus

Renal and urinary disorders

Not known: acute renal failure, incontinence

Reproductive system and breast disorders

Common: impotence

Not known: breast hypertrophy, gynaecomastia

General disorders and administration site conditions

Very Common: fatigue, fever

Common: peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome

Uncommon: generalized oedema  
Not known: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

#### Investigations

Common: WBC (white blood cell count) decreased, weight gain  
Uncommon: elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin  
Not known: blood glucose fluctuations in patients with diabetes

#### Injury and poisoning

Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

## **4.9 Overdose**

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is not usually required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other Antiepileptics  
ATC code: N03AX12

The precise mechanism of action of gabapentin is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives.

The binding site for gabapentin has been identified as the  $\alpha_2$ -delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including GABA<sub>A</sub>, GABA<sub>B</sub>, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100  $\mu$ M, which are not achieved *in vivo*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*.

Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years).

The data from this additional post-hoc analysis are summarised in the table below:

Response ( $\geq$ 50% improved) by treatment and age MITT* Population			
Age category	Placebo	Gabapentin	P-value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

\*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

## 5.2 Pharmacokinetic properties

### Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%.

Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 µg/ml and 20 µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N = 14)	
	Mean	% CV	Mean	% CV	Mean	% CV
C <sub>max</sub> (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
T <sub>max</sub> (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T <sub>1/2</sub> (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC <sub>0-t</sub> (µg.hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae <sup>0</sup> % (%)	NA	NA	47.2	(25)	34.4	(37)

C<sub>max</sub> = Maximum steady state plasma concentration

t<sub>max</sub> = Time for C<sub>max</sub>

T<sub>1/2</sub> = Elimination half-life

AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose

Ae<sup>0</sup>% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose

NA = Not available

### Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

### Metabolism

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

### Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

#### Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

### **5.3 Preclinical safety data**

#### Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

#### Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

#### Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m<sup>2</sup> of body surface area basis).

#### Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m<sup>2</sup> basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m<sup>2</sup> basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m<sup>2</sup> basis).

An increased incidence of hydronephrosis and/or hydroureter was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m<sup>2</sup> basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m<sup>2</sup> basis.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule Fill:

Maize starch  
Talc

#### Capsule Shell:

Yellow iron oxide (E172)  
Titanium dioxide (E171)  
Sodium lauryl sulfate  
gelatin

#### **Printing ink**

Shellac  
Propylene glycol  
Black iron oxide  
Potassium hydroxide

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.  
In use shelf life for HDPE bottle pack: 30 days

**6.4 Special precautions for storage**

Store below 25<sup>0</sup>C.

Blister pack: Store in the original package.

HDPE bottle pack: Store in the original container.

**6.5 Nature and contents of container**

Blister pack of Polyamide/Aluminium /PVC and Aluminium foil:  
10, 20, 30, 50, 60, 90, 100 and 200 capsules, hard.

HDPE bottle with polypropylene cap containing silica gel desiccant:  
100, 200 and 1000 capsules, hard.

Not all pack sizes may be marketed

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Aurobindo Pharma Limited  
Ares, Odyssey Business Park, West End Road  
South Ruislip HA4 6QD  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20532/0115

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23/12/2010

**10 DATE OF REVISION OF THE TEXT**

23/12/2010

**1 NAME OF THE MEDICINAL PRODUCT**

Gabapentin 400 mg capsules, hard

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 400 mg hard capsule contains 400 mg gabapentin.

For a full list of excipients, see section 6.1

**3 PHARMACEUTICAL FORM**

Capsule, hard

Gabapentin 400 mg capsules, hard, imprinted with 'D' on orange cap and '04' on orange body, containing white to off-white crystalline powder.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above (see section 5.1).

Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

**4.2 Posology and method of administration**

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1:

Dosing Chart – Initial Titration

Day 1 – 300 mg once a day

Day 2 – 300 mg two times a day

Day 3 - 300 mg three times a day

Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

### **Epilepsy**

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.

#### *Adults and adolescents:*

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

#### *Children aged 6 years and above:*

The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

### **Peripheral neuropathic pain**

#### *Adults*

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral

neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

#### **Instruction for all areas of indication**

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

#### Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

#### **Use in patients with renal impairment**

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

<b>Table 2</b>	
<b>Dosage of Gabapentin in adults based on renal function</b>	
<b>Creatinine Clearance (ml/min)</b>	<b>Total daily dose<sup>a</sup> (mg/day)</b>
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 <sup>b</sup> -600
< 15 <sup>c</sup>	150 <sup>b</sup> -300

<sup>a</sup> Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).

<sup>b</sup> To be administered as 300 mg every other day.

<sup>c</sup> For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

#### **Use in patients undergoing haemodialysis**

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

### **4.3 Contraindications**

Hypersensitivity to gabapentin or to any of the excipients.

#### **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 gabapentin

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

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

##### **Laboratory tests**

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Notice: The HDPE bottle contains desiccant. Do not swallow.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these anti-epileptic agents.

Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Coadministration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

#### **4.6 Pregnancy and lactation**

##### **Risk related to epilepsy and antiepileptic medicinal products in general**

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

##### **Risk related to gabapentin**

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

#### **4.7 Effects on ability to drive and use machines**

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

#### **4.8 Undesirable effects**

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency [very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ )]. Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

##### *Infections and infestations*

Very Common: Viral infection

Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

##### *Blood and the lymphatic system disorders*

Common: leucopenia

Not known: thrombocytopenia

##### *Immune system disorders*

Uncommon: allergic reactions (e.g. urticaria)

Not known: hypersensitivity syndrome, a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms

Metabolism and Nutrition Disorders

Common: anorexia, increased appetite

Psychiatric disorders

Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal

Not known: hallucinations

Nervous system disorders

Very Common: somnolence, dizziness, ataxia,

Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes

Uncommon: hypokinesia

Not known: other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders

Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders

Common: vertigo

Not known: tinnitus

Cardiac disorders

Uncommon: palpitations

Vascular disorder

Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders

Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence

Not known: pancreatitis

Hepatobiliary disorders

Not known: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne

Not known: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia, myalgia, back pain, twitching

Not known: myoclonus

Renal and urinary disorders

Not known: acute renal failure, incontinence

Reproductive system and breast disorders

Common: impotence

Not known: breast hypertrophy, gynaecomastia

General disorders and administration site conditions

Very Common: fatigue, fever

Common: peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome

Uncommon: generalized oedema  
Not known: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

#### Investigations

Common: WBC (white blood cell count) decreased, weight gain  
Uncommon: elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin  
Not known: blood glucose fluctuations in patients with diabetes

#### Injury and poisoning

Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

## **4.9 Overdose**

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is not usually required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other Antiepileptics

ATC code: N03AX12

The precise mechanism of action of gabapentin is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives.

The binding site for gabapentin has been identified as the alpha<sub>2</sub>-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including GABA<sub>A</sub>, GABA<sub>B</sub>, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100 µM, which are not achieved *in vivo*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*.

Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years).

The data from this additional post-hoc analysis are summarised in the table below:

Response (≥ 50% improved) by treatment and age MITT* Population			
Age category	Placebo	Gabapentin	P-value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

\*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

## 5.2 Pharmacokinetic properties

### Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%.

Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 µg/ml and 20 µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N = 14)	
	Mean	% CV	Mean	% CV	Mean	% CV
C <sub>max</sub> (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
T <sub>max</sub> (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T <sub>1/2</sub> (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC <sub>0-t</sub> (µg.hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae <sup>0</sup> % (%)	NA	NA	47.2	(25)	34.4	(37)

C<sub>max</sub> = Maximum steady state plasma concentration

t<sub>max</sub> = Time for C<sub>max</sub>

T<sub>1/2</sub> = Elimination half-life

AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose

Ae<sup>0</sup>% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose

NA = Not available

### Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

### Metabolism

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

### Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

#### Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

### **5.3 Preclinical safety data**

#### Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

#### Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

#### Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m<sup>2</sup> of body surface area basis).

#### Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25

times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m<sup>2</sup> basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m<sup>2</sup> basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m<sup>2</sup> basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m<sup>2</sup> basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m<sup>2</sup> basis.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule Fill:

Maize starch

Talc

#### Capsule Shell:

Red iron oxide (E172)

Yellow iron oxide (E172)

Titanium dioxide (E171)

Sodium lauryl sulfate

gelatin

#### **Printing ink**

Shellac

Propylene glycol

Black iron oxide

Potassium hydroxide

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

In use shelf life for HDPE bottle pack: 30 days

**6.4 Special precautions for storage**

Store below 25<sup>0</sup>C.

Blister pack: Store in the original package.

HDPE bottle pack: Store in the original container.

**6.5 Nature and contents of container**

Blister pack of Polyamide/Aluminium /PVC and Aluminium foil:  
10, 20, 30, 50, 60, 90, 100, 200 and 300 capsules, hard.

HDPE bottle with polypropylene cap containing silica gel desiccant:  
100, 200, 300 and 500 capsules, hard.

Not all pack sizes may be marketed

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Aurobindo Pharma Limited  
Ares, Odyssey Business Park, West End Road  
South Ruislip HA4 6QD  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20532/0116

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23/12/2010

**10 DATE OF REVISION OF THE TEXT**

23/12/2010

## Module 3

### Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

**Gabapentin 100 mg capsules, hard**  
**Gabapentin 300 mg capsules, hard**  
**Gabapentin 400 mg capsules, hard**  
Gabapentin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT GABAPENTIN IS AND WHAT IT IS USED FOR
2. BEFORE YOU TAKE GABAPENTIN
3. HOW TO TAKE GABAPENTIN
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE GABAPENTIN CAPSULES
6. FURTHER INFORMATION

#### 1. WHAT GABAPENTIN IS AND WHAT IT IS USED FOR

Gabapentin belongs to a group of medicines used to treat epilepsy and peripheral neuropathic pain (long lasting pain caused by damage to the nerves).

Gabapentin is used to treat:

Various forms of epilepsy (seizures that are initially limited to certain parts of the brain, whether the seizure spreads to other parts of the brain or not).

Your doctor will prescribe Gabapentin for you to help treat your epilepsy when your current treatment is not fully controlling your condition. You should take Gabapentin in addition to your current treatment unless told otherwise. Gabapentin can also be used on its own to treat adults and children over 12 years of age.

Peripheral neuropathic pain (long lasting pain caused by damage to the nerves). A variety of different diseases can cause peripheral neuropathic pain (primarily occurring in the legs and/or arms), such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles etc.

#### 2. BEFORE YOU TAKE GABAPENTIN

**DO NOT TAKE Gabapentin**

- if you are allergic (hypersensitive) to gabapentin or any of the other ingredients of Gabapentin.

Contact your doctor immediately if you become pregnant, think you might be pregnant or are planning to become pregnant while taking Gabapentin. Do not suddenly discontinue taking this medicine as this may lead to a breakthrough seizure, which could have serious consequences for you and your baby.

#### Breast-feeding:

Gabapentin, the active substance of Gabapentin, is passed on through human milk. Because the effect on the baby is unknown, it is not recommended to breast-feed while using Gabapentin.

#### Driving and using machines

Gabapentin may produce dizziness, drowsiness and tiredness. You should not drive, operate complex machinery or take part in other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

#### 3. HOW TO TAKE GABAPENTIN

Always take Gabapentin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will determine what dose is appropriate for you.

If you have the impression that the effect of Gabapentin is too strong or too weak, talk to your doctor or pharmacist as soon as possible.

If you are an elderly patient (over 65 years of age), you should take the normal dose of Gabapentin unless you have problems with your kidneys.

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.

Continue taking Gabapentin until your doctor tells you to stop

#### Method and Route of Administration

Gabapentin is for oral use. Always swallow the capsules whole with plenty of water.

#### Epilepsy, the usual dose is:

##### Adults and adolescents:

Take the number of capsules as instructed. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased as instructed by your doctor up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 separate doses, i.e. once in the morning, once in the afternoon and once in the evening.

##### Children aged 6 years and above:

The dose to be given to your child will be decided by your doctor as it is calculated against your child's weight. The treatment is started with a low initial dose which is gradually increased over a period of approximately 3 days. The usual dose to control epilepsy is 25-35 mg per kg per day. It is usually given in 3 separate doses, by taking the capsule(s) each day, usually once in the morning, once in the afternoon and once in the evening.

**Gabapentin is not recommended for use in children below 6 years**

#### Take special care with Gabapentin

- if you suffer from kidney problems your doctor may prescribe a different dosing schedule
- if you are on haemodialysis (to remove waste products because of kidney failure), tell your doctor
- if you develop muscle pain and/or weakness
- if you develop signs such as persistent stomach pain, feeling sick and being sick contact your doctor immediately as these may be symptoms of acute pancreatitis (an inflamed pancreas).

A small number of people being treated with anti-epileptics such as gabapentin have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Notice: The HDPE bottle contains desiccant. Do not swallow.

#### Taking other medicines

Please tell to your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription

#### Medicines containing morphine

If you are taking any medicines containing morphine, please tell your doctor or pharmacist as morphine may increase the effect of Gabapentin.

#### Antacids for indigestion

If Gabapentin and antacids containing aluminium and magnesium are taken at the same time, absorption of Gabapentin from the stomach may be reduced. It is therefore recommended that Gabapentin is taken at the earliest two hours after taking an antacid.

Gabapentin:

- is not expected to interact with other antiepileptic medicines or the oral contraceptive pill.
- may interfere with some laboratory tests, if you require a urine test tell your doctor or hospital that you are taking.

#### Taking Gabapentin with food and drink

Gabapentin can be taken with or without food.

#### Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

#### Pregnancy:

Gabapentin should not be taken during pregnancy, unless you are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential.

There have been no studies specifically looking at the use of gabapentin in pregnant women, but other medicines used to treat seizures have reported an increased risk of harm to the developing baby, particularly when more than one seizure medicine is taken at the same time. Therefore, whenever possible you should try to take only one seizure medicine during pregnancy and only under the advice of your doctor.

of age.

**Peripheral Neuropathic Pain the usual dose is:**

#### Adults:

Take the number of capsules as instructed by your doctor. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased as instructed by your doctor up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 separate doses, i.e. once in the morning, once in the afternoon and once in the evening.

#### If you have kidney problems or are receiving haemodialysis

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys or are undergoing haemodialysis.

#### If you take more Gabapentin than you should

Higher than the recommended doses may result in an increase in side effects including loss of consciousness, dizziness, double vision, slurred speech, drowsiness and diarrhoea. Call your doctor or go to the nearest hospital emergency unit immediately if you take more Gabapentin than your doctor prescribed. Take along any capsules that you have not taken, together with the container and the label so that the hospital can easily tell what medicine you have taken.

#### If you forget to take Gabapentin

If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take a double dose to make up for a forgotten dose.

#### If you stop taking Gabapentin

Do not stop taking Gabapentin unless your doctor tells you to. If your treatment is stopped it should be done gradually over a minimum of 1 week. If you stop taking Gabapentin suddenly or before your doctor tells you, there is an increased risk of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Gabapentin can cause side effects, although not everybody gets them.

**Contact your doctor immediately any of the following symptoms after taking this medicine as they can be serious:**

- **severe skin reactions that require immediate attention, such as swelling of the lips and face, skin rash and redness, and/or hair loss (these may be symptoms of a serious allergic reaction)**
- **persistent stomach pain, feeling sick and being sick as these may be symptoms of acute pancreatitis (an inflamed pancreas)**

If you are on haemodialysis, tell your doctor if you develop muscle pain and/or weakness.

Other side effects include:

**Very common side-effects (which may affect more than 1 person in 10):**

- Viral infection
- Feeling drowsy, dizziness, lack of coordination
- Feeling tired, fever

**Common side-effects (which may affect more than 1 person in 100):**

- Pneumonia, respiratory infection, urinary tract infection, inflammation of the ear or other infections
- Low white blood cell counts
- Anorexia, increased appetite
- Anger towards others, confusion, mood changes, depression, anxiety, nervousness, difficulty with thinking
- Convulsions, jerky movements, difficulty with speaking, loss of memory, tremor, difficulty sleeping, headache, sensitive skin, decreased sensation (numbness), difficulty with coordination, unusual eye movement, increased, decreased or absent reflexes
- Blurred vision, double vision
- Vertigo
- High blood pressure, flushing or dilation of blood vessels
- Difficulty breathing, bronchitis, sore throat, cough, dry nose
- Vomiting (being sick), nausea (feeling sick), problems with teeth, inflamed gums, diarrhoea, stomach pain, indigestion, constipation, dry mouth or throat, flatulence
- Facial swelling, bruises, rash, itch, acne
- Joint pain, muscle pain, back pain, twitching
- Difficulties with erection (impotence)
- Swelling in the legs and arms, difficulty with walking, weakness, pain, feeling unwell, flu-like symptoms
- Decrease in white blood cells, increase in weight
- Accidental injury, fracture, abrasion

Additionally in clinical studies in children, aggressive behaviour and jerky movements were reported.

**Uncommon side-effects (which may affect more than 1 person in a 1000):**

- Allergic reaction such as hives
- Decreased movement
- Racing heartbeat
- Swelling that may involve the face, trunk and limbs
- Abnormal blood test results suggesting problems with the liver.

**Since introduction to the market the following side-effects have been reported:**

- Decreased platelets (blood clotting cells)
- Hallucinations

#### **What Gabapentin looks like and contents of the pack**

Capsule, hard.

Gabapentin 100 mg capsules imprinted with 'D' on white cap and '02' on white body, containing white to off-white crystalline powder.

Gabapentin 300 mg capsules imprinted with 'D' on yellow cap and '03' on yellow body, containing white to off-white crystalline powder.

Gabapentin 400 mg capsules imprinted with 'D' on orange cap and '04' on orange body, containing white to off-white crystalline powder.

Gabapentin 100 mg capsules are available in:

- Blister polyamide/Aluminium/PVC and aluminium packs of 10, 20, 30, 50, 60, 90, 100 and 200 capsules, hard.
- HDPE bottle with polypropylene closure containing silica gel desiccant: 100, 200 and 1000 capsules, hard.

Gabapentin 300 mg capsules are available in:

- Blister polyamide/Aluminium/PVC and aluminium packs of 10, 20, 30, 50, 60, 90, 100 and 200 capsules, hard.
- HDPE bottle with polypropylene closure containing silica gel desiccant: 100, 200 and 1000 capsules, hard.

Gabapentin 400 mg capsules are available in:

- Blister polyamide/Aluminium/PVC and aluminium packs of 10, 20, 30, 50, 60, 90, 100, 200 and 300 capsules, hard.
- HDPE bottle with polypropylene closure containing silica gel desiccant: 100, 200, 300 and 500 capsules, hard.

Not all pack sizes may be marketed.

#### **Marketing Authorisation Holder**

Aurobindo Pharma Limited

Ares, Odyssey Business Park, West End Road

South Ruislip HA4 6QD

United Kingdom

#### **Manufacturer**

APL Swift Services (Malta) Limited

HF26, Hal Far Industrial Estate

Hal Far, Birzebbugia, BBG 3000

Malta

**This medicinal product is authorised in the Member States of the EEA under the following names:**

Austria	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg Hartkapseln
Belgium	Gabapentine Aurobindo 100 mg/ 300 mg/ 400mg, capsules, hard
Bulgaria	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg капсула, твърда
Czech Republic	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg tvrdé tobolky

- Problems with abnormal movements such as writhing, jerking movements and stiffness
- Ringing in the ears
- A group of side effects that could include swollen lymph nodes (isolated small raised lumps under the skin), fever, rash, and inflammation of liver occurring together.
- Yellowing of the skin and eyes (jaundice)
- Inflammation of the liver
- Acute kidney failure, incontinence
- Increased breast tissue, breast enlargement
- Adverse events following the abrupt discontinuation of gabapentin (anxiety, difficulty sleeping, feeling sick, pain, sweating), chest pain
- Blood glucose fluctuations in patients with diabetes.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### 5. HOW TO STORE GABAPENTIN CAPSULES

Keep out of the reach and sight of children.

Do not use Gabapentin after the expiry date, which is stated on the carton/label/bottle after EXP. The expiry date refers to the last date of that month.

Store below 25°C.

**Blisters pack:** Store in the original package.

**HDPE bottle pack:** Store in the original container.

Use within 30 days after first opening the HDPE bottle.

Medicines should not be disposed off via wastewater or household waste. Ask your pharmacist how to dispose off medicines no longer required. These measures will help to protect the environment.

#### 6. FURTHER INFORMATION

##### What Gabapentin contains

- The active substance is gabapentin.  
Each 100 mg hard capsule contains 100 mg gabapentin.  
Each 300 mg hard capsule contains 300 mg gabapentin.  
Each 400 mg hard capsule contains 400 mg gabapentin.

- The other ingredients are:

**Capsule contents:** Maize starch and talc.

**Capsule shell:**

100 mg: Titanium dioxide (E171), sodium lauril sulfate, gelatin.

300 mg: Yellow iron oxide (E172), titanium dioxide (E171), sodium lauril sulfate, gelatin.

400 mg: Red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), sodium lauril sulfate, gelatin.

**Printing ink:** Shellac, propylene glycol, black iron oxide, potassium hydroxide

Denmark	Gabapentin Aurobindo
Finland	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg kapseli, kova
France	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg, gélules
Germany	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg Hartkapseln
Greece	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg κάψακια, σκληρά
Hungary	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg kemény kapszula
Ireland	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg capsules, hard
Italy	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg capsule rigide
Latvia	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg cietās kapsulas
Lithuania	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg kietos kapsulės
Netherlands	Gabapentine Aurobindo 100 mg/ 300 mg/ 400mg, capsules, hard
Norway	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg kapsler, hard
Poland	Gabapentin Aurobindo
Portugal	Gabapentina Aurobindo
Romania	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg capsule
Slovak Republic	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg tvrdé kapsuly
Slovenia	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg trde capsule
Spain	Gabapentina Aurobindo 100 mg/ 300 mg/ 400mg cápsulas duras
Sweden	Gabapentin Aurobindo 100 mg/ 300 mg/ 400mg kapslar, hårda
United Kingdom	Gabapentin 100 mg/ 300 mg/ 400mg capsules, hard

This leaflet was last approved in 11/2010.

## Module 4

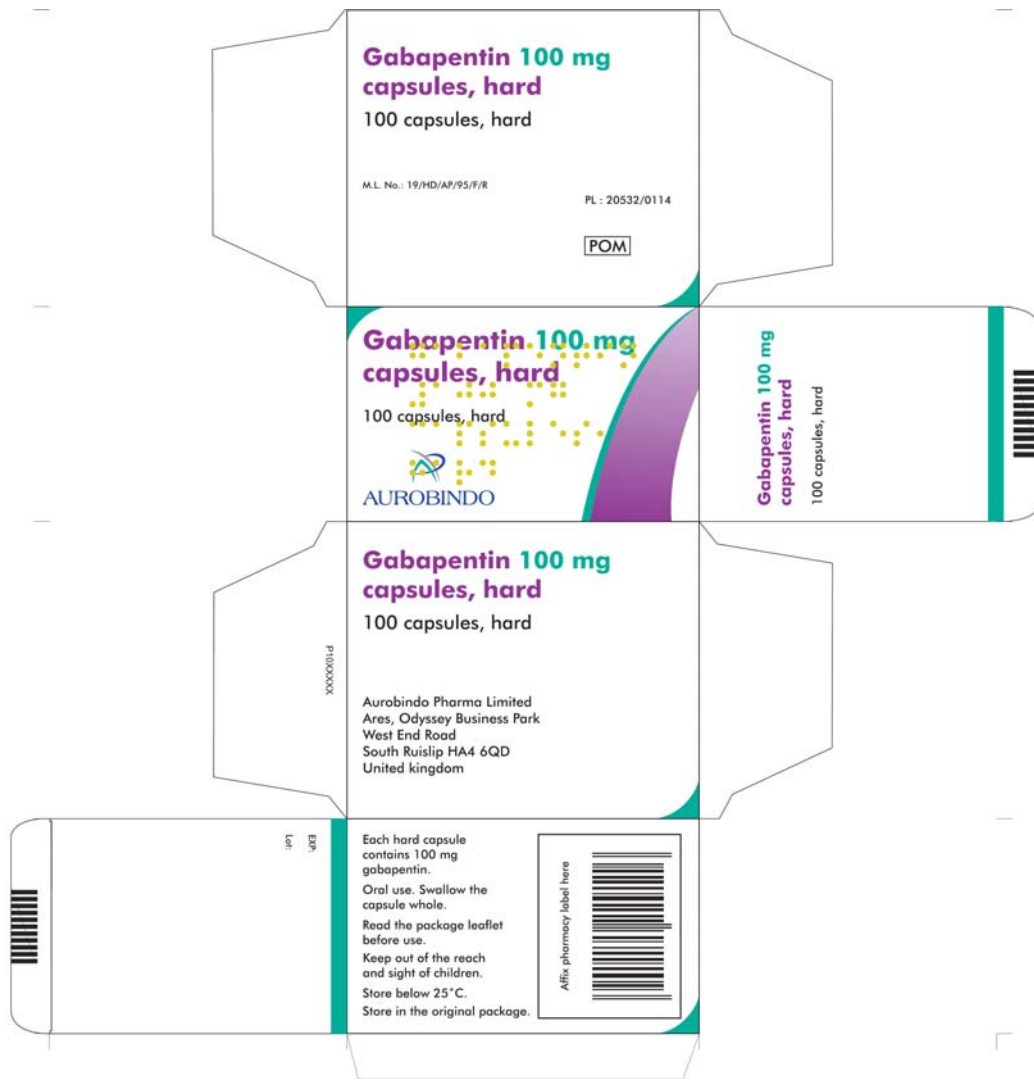
### Labelling

#### 100 mg capsules

#### Blister:

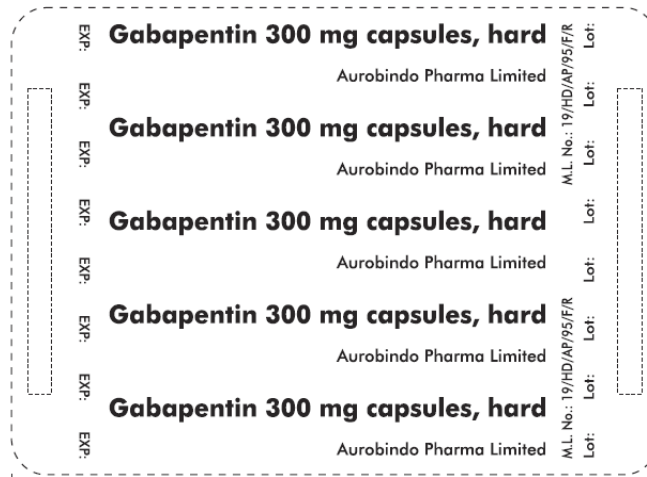


**Carton:**

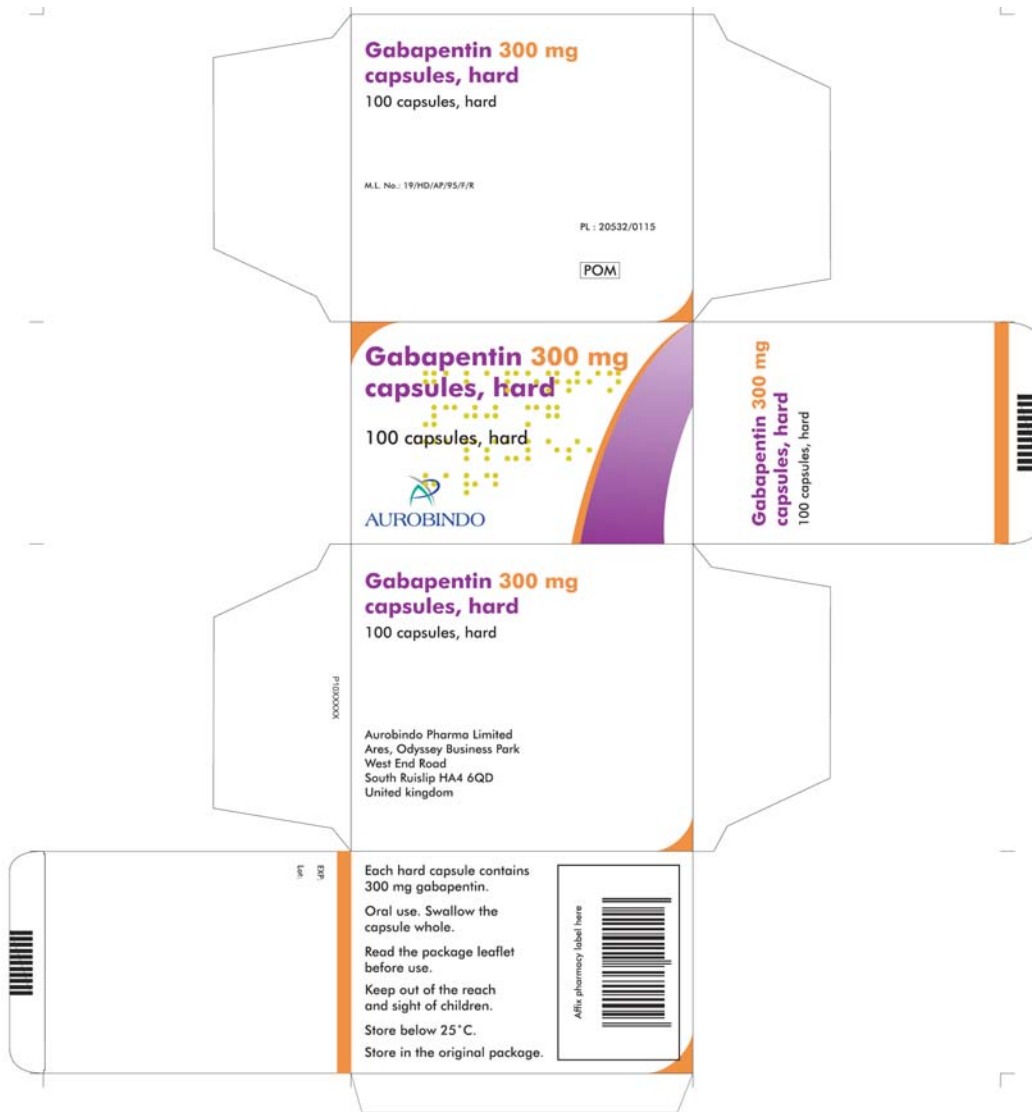


**300 mg capsules**

**Blister:**

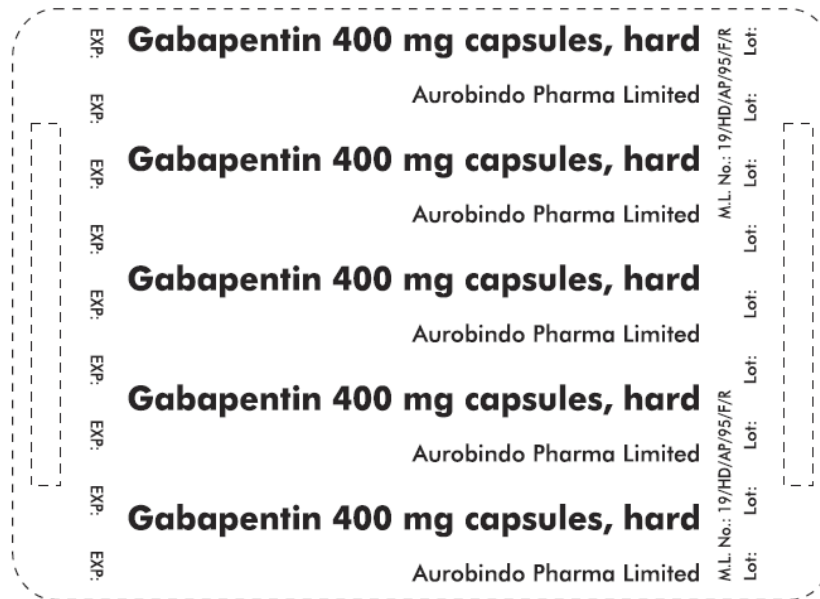


**Carton:**

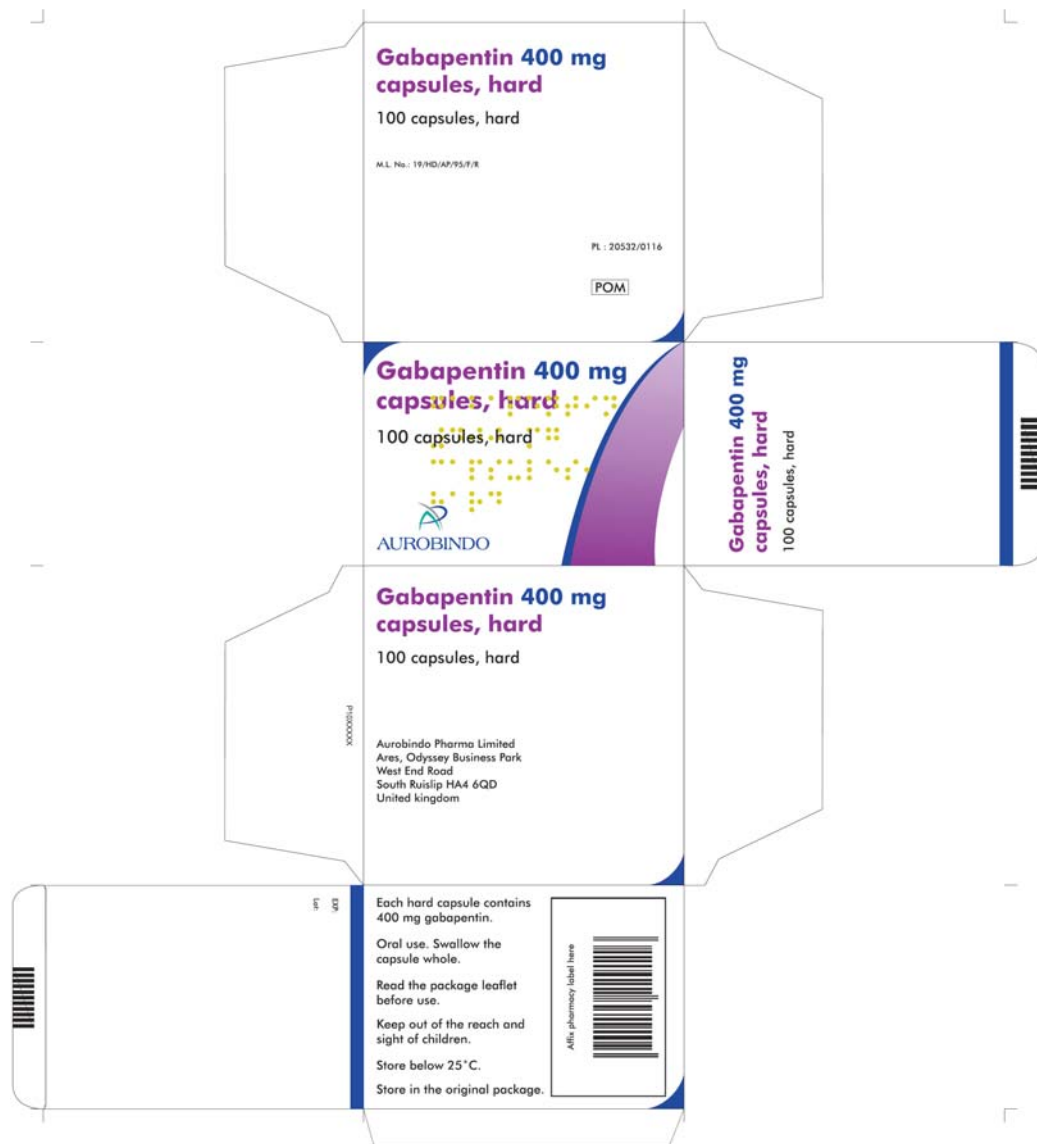


**400 mg capsules**

**Blister:**



**Carton:**



## Module 5

### Scientific Discussion

#### RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Gabapentin 100 mg, 300 mg and 400 mg capsules, hard in the treatment of epilepsy and peripheral neuropathic pain could be approved.

#### EXECUTIVE SUMMARY

##### Problem statement

These Decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that that the proposed products are generic versions of the products Neurontin 100 mg, 300 mg and 400 mg capsules, which are licensed to Pfizer AB, Sweden. These reference products were licensed in 1994 and have thus been authorised in the EU for more than 10 years, therefore the legal basis of these applications is acceptable.

With the UK as the Reference Member State in this Decentralised Procedure, Aurobindo Pharma Limited is applying for Marketing Authorisations for Gabapentin 100 mg, 300 mg and 400 mg capsules, hard in AT, BE, BG, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI and SK.

##### About the product

The precise mechanism of action of gabapentin is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses, including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. In vitro studies with radiolabeled gabapentin have characterized the binding site for gabapentin as the alpha2-delta subunit of voltage-gated calcium channels.

At clinical concentrations, gabapentin does not bind to other common drug or neurotransmitter receptors of the brain including GABAA, GABAB, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels in vitro and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems in vitro, but only at concentrations greater than 100 µM, which are not achieved in vivo. Gabapentin slightly reduces the release of monoamine neurotransmitters in vitro. Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures

from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

#### **General comments on the submitted dossier**

The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossiers regarding the quality, preclinical and clinical parts have been submitted.

#### **General comments on compliance with GMP, GLP, GCP and agreed ethical principles**

##### **GMP**

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

##### **GLP**

No new preclinical studies were submitted in support of these applications, and none are needed for applications of this type.

##### **GCP**

Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

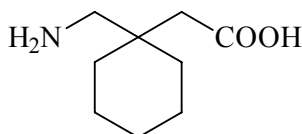
## SCIENTIFIC OVERVIEW AND DISCUSSION

### Quality aspects

#### Drug substance

##### General Information

rINN/USAN/BAN: Gabapentin  
Chemical name: 1-(aminomethyl)cyclohexaneacetic acid  
Chemical structure:



Molecular formula: C<sub>19</sub>H<sub>17</sub>NO<sub>2</sub>  
Molecular weight: 171.24

##### General properties

Physical form: White to off-white crystalline solid  
Solubility: Freely soluble in water, alkaline and acidic solutions  
Polymorphism: Gabapentin shows polymorphism  
pH: 6.5-8.0

There are no Ph. Eur. or BP monographs for gabapentin. The quality of the substance is suitably controlled by in-house specifications.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

### **Drug product**

The three different capsule strengths can be differentiated from each other by size, colour and identification markings. Gabapentin 100 mg capsules, hard are white and imprinted with 'D' and '02'; Gabapentin 300 mg capsules, hard are yellow and imprinted with 'D' and '03' and Gabapentin 400 mg capsules, hard are orange and imprinted with 'D' and '04'.

All three capsule strengths contain the excipients maize starch, talc, titanium dioxide (E171), sodium lauril sulfate, gelatin, shellac, propylene glycol, black iron oxide and potassium hydroxide. In addition, the 300 mg capsules contain yellow iron oxide (E172) and the 400 mg capsules contain red iron oxide (E172) and yellow iron oxide (E172).

The excipients used in the capsule fill comply with current Ph. Eur. monograph requirements. The ingredients of the gelatin capsule shells comply with either Ph. Eur., NF, EEC or USP requirements. Ingredients in the printing ink comply with Ph. Eur. requirements, where a Ph. Eur. monograph exists. Satisfactory in-house specifications are provided for the three capsule shell sizes used. Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided. Gelatin used in the manufacture of gelatin capsules is of bovine origin and is covered by a current EDQM certificate of suitability.

### **Pharmaceutical development**

The objective of the development programme was to develop a formulation similar to the innovator product, Neurontin 100 mg, 300 mg and 400 mg capsules. A satisfactory account of the pharmaceutical development has been provided.

### **Manufacturing process**

A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### **Finished product specification**

The finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

### **Container-closure system**

The finished products are stored in either blister packs of polyamide/aluminium /PVC and aluminium foil (in packs of 10, 20, 30, 50, 60, 90, 100 or 200 capsules, with the 400 mg capsules also coming in packs of 300) or HDPE bottles with polypropylene caps containing silica gel desiccant (containing either 100, 200 capsules, with the 100 mg and 300 mg capsules also coming in bottles of 1000 capsules and the 400 mg capsules also coming in bottles of 300 and 500 capsules).

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

### **Stability of the product**

Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for this product, with an in use shelf life for HDPE bottle pack of 30 days. The storage precautions 'Store in the original package' and Store in the original container should be applied to product stored in the blister packs and HDPE bottle packs, respectively as well as the precaution 'Store below 25<sup>0</sup>C'.

### **Product literature**

The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

### **Marketing Authorisation Application (MAA) forms**

The MAA forms are pharmaceutically satisfactory.

### **Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossiers.

### **Quality conclusion**

There are no objections to the approval of Gabapentin 100 mg, 300 mg and 400 mg capsules, hard from a quality point of view.

### **Preclinical aspects**

#### **Preclinical overview**

The pharmacological, pharmacokinetic and toxicological properties of gabapentin are well known. As gabapentin is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

#### **Expert report**

The preclinical overview has been written by a pharmacologist. The report refers to 29 publications up to the year 2007. In view of the fact that the pharmacotoxicological properties of gabapentin are well known, the overview is acceptable

#### **Environmental risk assessment**

A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto

the market is unlikely to result in an increase in the combined sales of all gabapentin - containing products, which in turn is unlikely to increase exposure of the environment to gabapentin.

### **Product literature**

The product literature is acceptable from a preclinical point of view.

### **Preclinical conclusion**

There are no objections to the approval of Gabapentin 100 mg, 300 mg and 400 mg capsules, hard from a preclinical point of view.

### **Clinical aspects**

#### **Pharmacokinetics**

To support the application, the applicant has submitted a single bioequivalence study: an open label, single dose, randomised, 2-way study of crossover design, performed under fasting conditions. The study was performed at the 400 mg dose strength. The company's clinical expert has provided the following justification for studying the 400 mg strength only, rather than both strengths:

- a. The pharmacokinetics of gabapentin are linear
- b. The qualitative composition of the three capsule strengths is the same
- c. The ratio between active substance and the excipients are the same across the different strengths
- d. The dissolution rate of the highest strength of the test product in-vitro is similar to that of the lower strengths, and the dissolution rate of all strengths of the test product in vitro are similar to the dissolution rates of the corresponding strengths of the reference product

Satisfactory justification is provided for a bio-waiver for Gabapentin 100 mg and 300 mg capsules. As Gabapentin 100 mg, 300 mg and 400 mg capsules, hard meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 400 mg strength capsules can be extrapolated to the 100 mg and 300 mg strength capsules.

#### **Study method**

Thirty-six healthy fasting male volunteers, aged 18-36 years, were randomised to receive a single dose of 400 mg orally of either the applicant's test product or the reference product (Neurontin 400 mg capsules). The randomisation scheme was balanced for sequence and appears random.

Plasma drug levels were followed for 48 hours following dosing and the schedule was appropriate for accurate determination of  $AUC_{inf}$  and  $C_{max}$ . The washout period between phases was sufficiently long at 12 days.

Thirty-three subjects completed the study. Three subjects were withdrawn: one subject was withdrawn during period 1 due to vomiting, one subject was withdrawn at period 2 for failing to turn up and one was withdrawn due to fever after period 1. The

reasons for these dropouts are satisfactory and the data were handled appropriately according to the study protocol.

Plasma samples were analysed to quantify the concentration of gabapentin using a validated LC/MS/MS bioanalytical method. The validation report has been provided.

The statistical methods used were ANOVA for AUC and  $C_{max}$ ; non-parametric for  $T_{max}$  and analysis of sequence/period effects.

## Results

Table 1. Pharmacokinetic parameters for parent drug (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$ , median, range). N=33.

Parameters	Statistics	Test (T)	Reference (R)
$C_{max}$ (ng/mL)	Arithmetic Mean	3099.40	3277.86
	S.D.	932.207	1249.424
	C.V. (%)	30.08	38.12
$AUC_{0-t}$ (hr. ng/mL)	Arithmetic Mean	31902.06	33407.04
	S.D.	10223.632	13671.960
	C.V. (%)	32.05	40.93
$AUC_{0-\infty}$ (hr. ng/mL)	Arithmetic Mean	32684.94	34231.39
	S.D.	10296.567	13815.283
	C.V. (%)	31.50	40.36
$T_{max}$ (hr)	Median	3.00	3.25
	S.D.	1.289	0.969
	C.V. (%)	40.31	30.49
$K_{el}$ (hr <sup>-1</sup> )	Arithmetic Mean	0.1150	0.1153
	S.D.	0.01091	0.01555
	C.V. (%)	9.49	13.49
$t_{1/2}$ (hr)	Arithmetic Mean	6.08	6.12
	S.D.	0.597	0.859
	C.V. (%)	9.82	14.04

Table 2. Pharmacokinetic parameters for parent drug (log-transformed values). N=33.

Parameters	Lnttransformed Data		
	(T/R) Ratio	90% Confidence Interval	Power
	(%)	(%)	(%)
$C_{max}$ (ng/mL)	96.25	89.47 - 103.54	99.92
$AUC_{0-t}$ (hr. ng/mL)	97.43	91.68 - 103.55	100.00
$AUC_{0-\infty}$ (hr. ng/mL)	97.40	91.87 - 103.27	100.00

These results are within conventional bioequivalence criteria, with the 90% confidence intervals between 80-125%.

## Conclusion

Based on the submitted bioequivalence study Gabapentin 400 mg capsules, hard are considered bioequivalent to Neurontin 400 mg capsules.

As Gabapentin 100 mg, 300 mg and 400 mg capsules, hard meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 400 mg strength capsules can be extrapolated to the 100 mg and 300 mg strength capsules.

#### **Pharmacodynamics**

The pharmacodynamic characteristics of gabapentin have been well-studied in the past. There would be no particular concerns for a generic medicinal product. No new data have been submitted and none are required.

#### **Clinical efficacy and safety**

No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of gabapentin.

#### **Pharmacovigilance system**

The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

#### **Risk management plan**

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for these applications.

#### **Expert report**

A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.

#### **Product literature**

All product literature (SmPCs, PIL and labelling) is medically satisfactory.

#### **Clinical conclusion**

There are no objections to the approval of Gabapentin 100 mg, 300 mg and 400 mg capsules, hard from a clinical point of view.

## **OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

### **QUALITY**

The important quality characteristics of Gabapentin 100 mg, 300 mg and 400 mg capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of these type.

### **EFFICACY**

The use of gabapentin in the treatment of epilepsy and peripheral neuropathic pain is well established. Bioequivalence has been demonstrated between the applicant's Gabapentin 100 mg, 300 mg and 400 mg capsules, hard and the reference products. New efficacy data is, therefore, not needed.

### **SAFETY**

No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

### **RISK-BENEFIT ASSESSMENT**

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with gabapentin is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is, therefore, considered to be positive. Marketing Authorisations should be granted.