

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Gabapentin Aurobindo 400 mg capsules, hard

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 mg gabapentin.

Excipients of known effect: each hard capsule contains 90.0 mg lactose.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard.

The 400 mg capsules are orange in colour and contain a white powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Epilepsy

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

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

#### Treatment of peripheral neuropathic pain

Gabapentin Aurobindo 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

#### Posology

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.

<b>Table 1</b>		
Dosing Chart – Initial Titration		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	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.

#### *Elderly (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.

#### *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>	
Dosage of gabapentin in adults based on renal function	
Creatinine Clearance (mL/min)	Total Daily Dose <sup>a</sup> (mg/day)
≥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> The 150mg daily dose 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.

#### 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).

### **4.3 Contraindications**

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

### **4.4 Special warnings and precautions for use**

#### Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug rash with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with gabapentin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gabapentin should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of gabapentin, treatment with gabapentin must not be restarted in this patient at any time.

#### Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis (see section 4.8).

#### Suicidal ideation and behaviour

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. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin in the post-marketing experience (see section 4.8).

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

#### Acute pancreatitis

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

#### Seizures

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

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

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one antiepileptic, 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.

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been post-marketing reports of confusion, loss of consciousness and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

#### Myasthenia gravis

Gabapentin should be used with caution in patients with myasthenia gravis as post-marketing cases of exacerbation of myasthenia gravis have been reported with gabapentin.

#### Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids, should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or concomitant treatment with CNS depressants including opioids should be reduced appropriately (see section 4.5).

Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a population-based, observational, nested case-control study of opioid users, co-prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88,  $p < 0.001$ ]).

#### Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

#### Elderly (over 65 years of age)

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.

#### Paediatric population

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.

#### Misuse, abuse potential and dependence

Gabapentin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for gabapentin misuse, abuse and dependence, and gabapentin should be used with caution in such patients. Before prescribing gabapentin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.

Patients treated with gabapentin should be monitored for symptoms of gabapentin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

#### Withdrawal symptoms

After discontinuation or dose reduction of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed (see section 4.8). The patient should be informed about this at the start of the treatment. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise. The occurrence of withdrawal symptoms may indicate drug dependence. If gabapentin should be discontinued or the dose reduced, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.2).

#### 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.

#### Lactose

Gabapentin Aurobindo capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### Sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

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

There are spontaneous and literature case reports of respiratory depression, sedation and death associated with gabapentin when co-administered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of gabapentin with opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those with substance abuse disorders.

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 who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid 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 antiepileptic agents.

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

Co-administration 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 co-administered with cimetidine is not expected to be of clinical importance.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

##### Risk related to epilepsy and antiepileptic drugs (AEDs) in general

Specialist advice regarding the potential risk to a foetus caused by both seizures and antiepileptic treatment should be given to women of childbearing potential, and especially to women planning for pregnancy and women who are pregnant. The need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, 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. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the antiepileptics used.

##### Risk related to gabapentin

Gabapentin crosses the human placenta.

Data from a Nordic observational study of more than 1700 pregnancies exposed to gabapentin in the first trimester showed no higher risk of major congenital malformations among the children exposed to gabapentin compared to the unexposed children and compared to the children exposed to pregabalin, lamotrigine and pregabalin or lamotrigine. Likewise, no increased risk of neurodevelopmental disorders was observed in children exposed to gabapentin during pregnancy.

There was limited evidence of a higher risk of low birth weight and preterm birth but not of stillbirth, small for gestational age, low Apgar score at 5 minutes and microcephaly in newborns of women exposed to gabapentin.

Studies in animals have shown reproductive toxicity (see section 5.3).

Gabapentin can be used during the first trimester of pregnancy if clinically needed.

Neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome. Newborns should be monitored carefully.

#### Breast-feeding

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.

#### Fertility

There is no effect on fertility in animal studies (see section 5.3).

### **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 ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ), very rare ( $< 10\ 000$ ) and not known (cannot be estimated from the available data)). 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 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), anaphylaxis (see section 4.4)*

#### *Metabolism and nutrition disorders*

Common: Anorexia, increased appetite

Uncommon: hyperglycaemia (most often observed in patients with diabetes)

Rare: hypoglycaemia (most often observed in patients with diabetes)

Not known: *hyponatraemia*

*Psychiatric disorders*

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

Uncommon: agitation

Not known: *Suicidal ideation, Hallucinations, drug dependence*

*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, mental impairment

Rare: Loss of consciousness

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 disorders*

Common: Hypertension, vasodilatation

*Respiratory, thoracic and mediastinal disorders*

Common: Dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Rare: Respiratory depression

*Gastrointestinal disorders*

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

Uncommon: Dysphagia

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, toxic epidermal necrolysis, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)*

*Musculoskeletal and connective tissue disorders*

Common: Arthralgia, myalgia, back pain, twitching

Not known: *Rhabdomyolysis, myoclonus, exacerbation of myasthenia gravis*

*Renal and urinary disorders*

Not known: *Acute renal failure, incontinence*

*Reproductive system and breast disorders*

Common: Impotence

Not known: *Breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)*

*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\**, 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 creatine phosphokinase increased*

#### *Injury, poisoning and procedural complications*

Common: Accidental injury, fracture, abrasion

Uncommon: Fall

\* After discontinuation or dose reduction of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed. Withdrawal symptoms may occur shortly after discontinuation or dose reduction, usually within 48 hours (see section 4.4).

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.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, website: [www.hpra.ie](http://www.hpra.ie).

## **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, loss of consciousness, 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, minimise 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 usually not 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 groups: Other Analgesics and Antipyretics, Gabapentinoids ATC code: N02BF01

#### Mechanism of action

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the  $\alpha 2\delta$  (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the  $\alpha 2\delta$  subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than  $\alpha 2\delta$ .

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to  $\alpha 2\delta$  through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the  $\alpha 2\delta$  subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centers through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

#### Clinical efficacy and safety

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  $\mu\text{g/mL}$  and 20  $\mu\text{g/mL}$  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
$C_{\text{max}}$ ( $\mu\text{g/mL}$ )	4.02	(24)	5.74	(38)	8.71	(29)
$t_{\text{max}}$ (hr)	2.7	(18)	2.1	(54)	1.6	(76)
$T_{1/2}$ (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) ( $\mu\text{g}\cdot\text{hr/mL}$ )	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

$C_{\text{max}}$  = Maximum steady state plasma concentration

$t_{\text{max}}$  = Time for  $C_{\text{max}}$

$T_{1/2}$  = 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.

### Biotransformation

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.

In a pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower  $C_{max}$  and higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

#### 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  $T_{1/2}$ ), 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  $mg/m^2$  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  $mg/m^2$  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 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  $mg/m^2$  basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately ½ 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 pregnant rabbits given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 0.3 to 8 times the daily human dose of 3600 mg on a mg/m<sup>2</sup> basis. The margins of safety are insufficient to rule out the risk of these effects in humans.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Capsule content:

Lactose

Maize starch

Talc

Capsule Shell:

Gelatin

Titanium dioxide (E171)

Sodium lauryl sulphate

Iron oxide red (E172) and iron oxide yellow (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

PVC- Aluminium blister: 3 years

HDPE- Bottle: 3 years

### **6.4 Special precautions for storage**

Do not store above 25°C.

### **6.5 Nature and contents of container**

There are two packaging presentations:

PVC – Alu blister

Containing 10, 20 (also as sample), 30, 50, 90, 100, 200 (2x100), 250 capsules

*As hospital pack only:* 500 (5x100), 1000 (10x100) capsules.

*Unit dose:* 20x1, 60x1, 100x1 capsules.

White HDPE bottle with white screw closure.

Containing 50, 100, 250 capsules.

Not all pack sizes may be marketed.

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

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Aurobindo Pharma (Malta) Limited  
Vault 14, Level 2, Valletta Waterfront  
Floriana  
FRN 1913  
Malta

**8 MARKETING AUTHORISATION NUMBER**

PA1445/025/003

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

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Date of last renewal: 18 November 2010

**10 DATE OF REVISION OF THE TEXT**

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