

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gabapentin Rosemont 50mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 50mg Gabapentin.

Excipients with known effect:

Methyl parahydroxybenzoate – 1.2mg/1ml

Ethyl parahydroxybenzoate – 0.6mg/1ml

Potassium – 3.8mg/1ml

Sodium – 0.72mg/1ml

Propylene glycol - 35mg/1ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

A clear, colourless solution

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

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.

Table 1

Dosing chart – initial titration

| Day 1 | Day 2 | Day 3 |
|-------------------------|------------------------------|--------------------------------|
| 300 mg (6ml) once a day | 300 mg (6ml) two times a day | 300 mg (6ml) 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 (18ml – 72ml). Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg (6ml) 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 (6ml) increments every 2-3 days up to a

maximum dose of 3600 mg/day (72ml). Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day (36ml) is one week, to reach 2400 mg/day (48ml) is a total of 2 weeks, and to reach 3600 mg/day (72ml) is a total of 3 weeks. Dosages up to 4800 mg/day (96ml) 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 (18ml) given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day (6ml) increments every 2-3 days up to a maximum dose of 3600 mg/day (72ml). Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day (36ml) is one week, to reach 2400 mg/day (48ml) is a total of 2 weeks, and to reach 3600 mg/day (72ml) 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.

Physicians should be cautious in prescribing high doses of gabapentin to young adolescents or adults with low body weight (39 – 50Kg) as in these patients the levels of propylene glycol, acesulfame K and saccharin sodium may exceed the recommended WHO daily intake limits.

| | | mg/kg/day based on maximum dose of 3600mg | |
|------------------|------------------------|---|-------------|
| | WHO daily intake limit | Average 12 year old (39Kg) | 50Kg person |
| Acesulfame K | 15mg/kg/day | 36.9mg | 28.8mg |
| Saccharin Sodium | 5mg/kg/day | 6.5mg | 5.0mg |
| Propylene Glycol | 25mg/kg/day | 64.6mg | 50.4mg |

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.

Table 2
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION

| Creatinine Clearance (ml/min) | Total Daily Dose ^a (mg/day) |
|-------------------------------|--|
| ≥80 | 900-3600 (18-72ml) |
| 50-79 | 600-1800 (12- 36ml) |
| 30-49 | 300-900 (6ml-18ml) |
| 15-29 | 150 ^b -600 (3ml-12ml) |
| <15 ^c | 150 ^b -300 (3ml-6ml) |

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

^b To be administered as 300 mg (6ml) every other day.

^c 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 (6ml-8ml), then 200 to 300 mg (4ml-6ml) 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.

Suitable for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes only. For further information see section 6.6.

Gabapentin can be given with or without food.

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

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking antiepileptic drugs including gabapentin (see section 4.8). It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

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 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.

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 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. Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been postmarketing 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.

Concomitant use with opioids

Patients who require concomitant treatment with opioids should be carefully observed for signs of central nervous system (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 opioids should be reduced appropriately (see section 4.5).

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.

Use in elderly patients (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.

Abuse and Dependence

Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behavior, dose escalation, development of tolerance.

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.

Excipient warnings

This product contains:

- Parahydroxybenzoates. These may cause allergic reactions (possibly delayed).
- Potassium – 3.8mg per 1ml dose. This should be taken into consideration for patients with reduced kidney function or patients on controlled potassium diets.
- Sodium – 0.72mg per 1ml dose. This should be taken into consideration for patients on a controlled sodium diet. This is equivalent to 0.04% of the WHO recommended maximum daily intake of 2g sodium for an adult.
- Propylene glycol – 35mg per 1 ml dose. This should be taken into consideration for pregnant or breast-feeding women, patients who suffer from liver or kidney disease and children under 5, particularly if the child uses other medicines that contain propylene glycol or alcohol.

4.5 Interaction with other medicinal products and other forms of interactions

There are spontaneous and literature case reports of respiratory depression and/or sedation associated with gabapentin and opioid use. In some of these reports, the authors considered this a particular concern with the combination of gabapentin and opioids, especially in elderly patients.

In a study involving healthy volunteers (N=12), when a 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg 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 opioids 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 Fertility, pregnancy and lactation

Pregnancy

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 practised 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.

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 ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); very rare ($< 1/10000$). 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.

| Body System | Adverse drug reactions |
|--|--|
| 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 | <i>thrombocytopenia</i> |
| Immune system disorders | |
| Uncommon | allergic reactions (e.g. urticaria) |
| Not known | <i>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)</i> |
| Metabolism and Nutrition Disorders | |
| Common | anorexia, increased appetite |
| Uncommon | hyperglycemia (most often observed in patients with diabetes) |
| Rare | hypoglycemia (most often observed in patients with diabetes) |
| Not known | hyponatremia |
| Psychiatric disorders | |
| Common | hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal |
| Uncommon | agitation |
| Not known | <i>hallucinations</i> |
| 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 | <i>other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)</i> |
| Eye disorders | |
| Common | visual disturbances such as amblyopia, diplopia |
| Ear and Labyrinth disorders | |
| Common | vertigo |
| Not known | <i>tinnitus</i> |
| 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 | <i>pancreatitis</i> |

Hepatobiliary disorders

| | |
|-----------|----------------------------|
| Not known | <i>hepatitis, jaundice</i> |
|-----------|----------------------------|

Skin and subcutaneous tissue disorders

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

| | |
|-----------|---|
| Not known | <i>Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)</i> |
|-----------|---|

Musculoskeletal and connective tissue disorders

| | |
|--------|---|
| Common | arthralgia, myalgia, back pain, twitching |
|--------|---|

| | |
|-----------|----------------------------------|
| Not known | <i>rhabdomyolysis, myoclonus</i> |
|-----------|----------------------------------|

Renal and urinary disorder

| | |
|-----------|--|
| Not known | <i>acute renal failure, incontinence</i> |
|-----------|--|

Reproductive system and breast disorders

| | |
|--------|-----------|
| Common | impotence |
|--------|-----------|

| | |
|-----------|--|
| Not known | <i>breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)</i> |
|-----------|--|

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 | <i>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.</i> |
|-----------|--|

Investigations

| | |
|--------|---|
| Common | WBC (white blood cell count) decreased, weight gain |
|--------|---|

| | |
|----------|--|
| Uncommon | elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin |
|----------|--|

| | |
|-----------|---|
| Not known | <i>blood glucose fluctuations in patients with diabetes, blood creatine phosphokinase increased</i> |
|-----------|---|

Injury, poisoning and procedural complications

| | |
|--------|---------------------------------------|
| Common | accidental injury, fracture, abrasion |
|--------|---------------------------------------|

| | |
|----------|------|
| Uncommon | fall |
|----------|------|

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 the national reporting systems.

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

Dublin 2

IRL

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 grams. 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 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: Antiepileptics, Other antiepileptics

ATC Code: N03AX12

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 target 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.

50mg/ml Oral Solution

A bioequivalence study was performed on Gabapentin 50mg/ml Oral Solution against the brand leaders 300mg capsules. Data is provided below to show that the two products are bioequivalent and interchangeable mg for mg.

Gabapentin 50mg/1ml Oral Solution vs Gabapentin 300mg Capsules

| | AUC _{0-t} | AUC _{0-inf} | C _{max} |
|---------------------------------|--------------------|----------------------|-------------------|
| Ratio ¹ | 96.88% | 96.99% | 99.20% |
| 90% Geometric C.I. ² | 90.69% to 103.50% | 90.99% to 103.38% | 91.61% to 107.41% |
| Intra-Subject CV | 13.68% | 13.22% | 16.51% |

¹ Calculated using least-squares means according to the formula: $e^{(\text{Gabapentin Solution} - \text{Gabapentin capsules})} \times 100$

² 90% Geometric Confidence Interval using In-transformed data.

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 CL_r 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 tumours 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 tumours 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 tumours 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/m² 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/m² 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/m² basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m² 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/m² 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/m² basis.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Acesulfame potassium (E950)

Saccharin sodium

Propylene glycol (E1520)

Methyl parahydroxybenzoate (E218)

Ethyl parahydroxybenzoate (E214)

Carmellose Sodium (E466)

Aniseed flavour (containing flavouring preparations, isopropyl alcohol and water)

Purified water

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

1 year

1 month once open

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Bottle: Amber (Type III) glass with capacity of 150ml

Pack size: 150ml or 3 x 150ml – not all pack sizes may be marketed

Closure: HDPE, EPE wadded, tamper evident, child resistant screw on cap

Syringe: LDPE body, polystyrene plunger with a capacity of 10ml, graduated at each 1ml and intermediate marks every 0.5ml

Bottle adaptor: Low Density Polyethylene

6.6 Special precautions for disposal

Instructions for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes.

Gabapentin Oral Solution is suitable for use with the following type of NG and PEG tubes:

| Material | External Bore Size (Fr Unit) | Internal Diameter (mm) | Maximum Length (cm) | Recommended flush volume |
|--------------|------------------------------|------------------------|---------------------|--------------------------|
| Silicone | 4 | 0.8 | 125 | 5mL |
| | 6 | 1.0 | 125 | 5mL |
| | 10 | 2.0 | 125 | 10mL |
| PVC | 4 | 0.8 | 125 | 5mL |
| | 8 | 1.5 | 125 | 5mL |
| | 12 | 2.5 | 125 | 10mL |
| Polyurethane | 4 | 0.8 | 125 | 5mL |
| | 8 | 1.5 | 125 | 5mL |
| | 12 | 2.6 | 125 | 10mL |
| | 18 | 4.00 | 75 | 10mL |

Ensure that the enteral feeding tube is free from obstruction before administration.

- 1.Flush the enteral tube with water, using the minimum flush volume required.
- 2.Administer the required dose of Gabapentin Oral Solution with a suitable measuring device. The oral syringe included in the pack is only for patients who are able to swallow the medicine. HCPs must use another suitable device.
- 3.Flush the enteral tube with water again using the minimum flush volume required.

This product should be administered with silicone, PVC, polyurethane NG or PEG tubes **only**.

Healthcare professional should be aware that with air flushing procedure there is a risk of under dosing (up to 50%). It is therefore recommended that only water flush is used.

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

7 MARKETING AUTHORISATION HOLDER

Taw Pharma (Ireland) Ltd
104 Lower Baggot Street
Dublin 2
Dublin
D02 Y940
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23081/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21st August 2018

10 DATE OF REVISION OF THE TEXT

February 2021