1. NAME OF THE MEDICINAL PRODUCT

Gabapentin Athlone 300mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300mg gabapentin.
Each capsule contains 40.0mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Size 1, yellow, hard gelatin capsules, with white powder. Marked with 'GABA 300mg'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Neuropathic Pain
Gabapentin capsules are indicated for the treatment of peripheral neuropathic pain in adults, e.g. painful diabetic neuropathy and post herpetic neuralgia.

Children under 6 years of age
The use of gabapentin is not recommended in children under 6 years of age.

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**
300mg once a day	300mg two times a day	300mg 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.

Table 2

DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION

Creatine Clearance (ml/min)	**Total Daily Dose [a] (mg/day)**
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 [b] -600
≤15 [c]	150 [b] -300

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 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, 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 gabapentin or to any of the excipients.

4.4 Special warnings and precautions for use

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

Patients who develop acute pancreatitis during treatment with gabapentin, should be considered for discontinuation of therapy (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). When, in the judgement of the clinician, there is a need for dose reduction, discontinuation or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

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 achieve gabapentin monotherapy by withdrawing concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic have a low success rate.

Gabapentin is not generally considered effective in the treatment of primary generalised 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).

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 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.

Patients taking gabapentin can be the subject of mood and behavioural disturbance. Such reports have been noted in patients on gabapentin although a causal link has not been established.

Caution is recommended in patients with a history of psychotic illness. On commencing gabapentin therapy, psychotic episodes have been reported in some patients with, and rarely without, a history of psychotic illness. Most of these events resolved when gabapentin was discontinued or the dosage was reduced.

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 benefit 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 behaviour, dose escalation, development of tolerance.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophila 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.

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 outset.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 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, sedation and respiratory depression and the dose of gabapentin or morphine should be reduced appropriately.

Gabapentin may be used in combination with other anti-epileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other anti-epileptic drugs.

There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine or phenobarbitone. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

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

The co-administration of gabapentin with aluminium and magnesium containing antacids reduces the bioavailability of gabapentin by up to 24%. It is recommended that gabapentin is taken two hours after antacid administration.

The co-administration of gabapentin with morphine is reported to increase gabapentin AUC by more than 40%. Coadministration with hydrocodone also seems to increase gabapentin AUC, but to a lesser extent. Patients should therefore be monitored for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately. The pharmacokinetics of morphine and hydrocodone seem to be unaffected by gabapentin.

The slight decrease in renal excretion of gabapentin observed when co-administered with cimetidine is not expected to be of clinical importance.

Renal excretion of gabapentin is unaltered by probenecid.

Food has no affect on Gabapentin pharmacokinetics.

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 be 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 women 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 be used during pregnancy only if the potential benefit to the patient justifies 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. The effect on the nursing infant is unknown. Therefore during lactation it should be administered with caution. Gabapentin should be used during lactation only if the potential benefit to the mother clearly justifies the potential risk to the breast fed infant.

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. These otherwise mild or moderate adverse events could be potentially dangerous in patients driving or operating machinery, particularly until such time as the individual patient's experience with the drug is established. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

Since gabapentin has most often been administered in combination with other anti-epileptic agents, it is not possible to determine which agents, if any are associated with adverse events. 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 (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, 1<100),rare (≥1/10000, <1/1000) and very rare (< 1/10,000)).
Where an adverse event 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	*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
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
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, 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
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, 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, drug rash with eosinophilia and systemic (see section 4.4)*
Musculoskeletal, connective tissue and bone disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	*Myoclonus, rhabdomyolysis*
Renal and urinary disorder	
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 (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 creatine phosphokinase increased*
Injury and poisoning	
Common	accidental injury, fracture, abrasion
Uncommon	fall

During treatment with gabapentin cases of acute pancreatitis were reported. Relationship to 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 hyperkinesis 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Acute, life threatening toxicity has not been observed with gabapentin overdose of up to 49g. 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. Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. Therefore, reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdose.

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

Although gabapentin can be removed by haemodialysis it is not usually required. However, in-patients with 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 include ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Antiepileptics, Other antiepileptics ATC code: N03AX12

Mechanism of Action
Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several drugs that interact with GABA synapses, including valproate, barbiturates, benzodiazepines, GABA transminase inhibitors, GABA uptake inhibitors, GABA antagonist and GABA prodrugs. In vitro studies with radiolabelled gabapentin have revealed a new peptide binding site in areas of rat brain including the neocortex and the hippocampus which could be related to the anticonvulsant activity of gabapentin and its structural derivatives. Nevertheless, the identification and function of these gabapentin binding sites remains to be elucidated. The binding site for gabapentin has been identified as the $alpha_2$-delta subunit of voltage-gated calcium channels. At therapeutic concentrations, gabapentin does not bind to the receptors of other common drugs or brain neurotransmitter receptors including $GABA_{A,}$ $GABA_{B,}$ benzodiazepines, glutamate, glycine or N-methyl-d-aspartate.

Gabapentin differs from phenytoin and carbamazepine in that it does not interact with the sodium channels *in vitro*. Gabapentin partially reduces the agonist response of glutamate N-methyl-D-asparate (NMDA) in some *in vitro* assay systems, but only at concentrations of over 100 µm, which are not

reached in vivo. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro.* The administration of gabapentin to rats increased GABA exchange in various areas of the brain in a similar way to sodium valproate, but in different areas of the brain. The importance of these different actions of gabapentin for its anticonvulsive effects has not been established. In animals, gabapentin readily enters the brain and perverts seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures

Clinical efficacy and safety

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects ranging in age from 3-12 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 2-3 hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300mg 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 2µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy Pharmacokinetic parameters are given in Table 3.

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

Table 3						
Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration						
Pharmacokinetic parameter	300mg (N = 7)		400mg (N = 14)		800mg (N = 14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{max}µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)

t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) μg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	N/A	N/A	47.2	(25)	34.4	(37)

C_{max} = Maximum steady state plasma concentration
t_{max} = Time for C_{max}
T1/2 = 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 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 Cmax 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 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 tumours was found only in male rats at the highest dose. Peak plasma drug concentrations and areas under the concentration time curve in rats at 2000 mg/kg is 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 metastasise 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 therefore of uncertain significance.

Mutagenesis

Gabapentin has no genotoxic potential. It was not mutagenic in standard *in vitro* assays using mammalian cells or bacteria. Gabapentin did not induce structural chromosome aberrations in mammalian cells in vitro or in vivo, and did not induce micronucleus formation on 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 of 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 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^2 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^2 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^2 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 ¼ to 8 times the daily human dose of 3600 mg on a mg/m^2 basis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Titanium dioxide (E171)
Yellow Iron Oxide (E172)
Gelatin

Printing ink:
Shellac
Black iron oxide (E172)
Soya lecithin
Antifoam

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/Al blister pack supplied in packs of 100 capsules, each blister strip contains 10 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited
Ballymurray,
Co.Roscommon,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 30464/0095

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/02/2007

10 DATE OF REVISION OF THE TEXT

20/05/2016