PRODUCT NAME	GABAPENTIN CAPSULES
GENERIC NAME	Gabapentin Capsules USP 300 mg

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

GABAPENTIN CAPSULES USP 300 MG

2. Qualitative and quantitative composition

2.1 Label Claim

Each hard gelatin capsule contains:
Gabapentin USP 300 mg
Excipients q.s.
Colour: Approved colours used in empty capsule shells

2.2 Quantitative Composition

Batch Size: 3.06 Lac Capsules

Sr. No.	Ingredients	Claim	Spec.	Qty/Cap (mg)	(%) Overages	Qty./306000 Capsules (Kg)
1.	Gabapentin	300 mg	USP	300.00	NIL	91.800
1.	Sodium Starch Glycolate	-	BP	5.00	NIL	1.530
2.	Magnesium Stearate	-	BP	2.00	NIL	0.613
3.	Colloidal Anhydrous Silica	-	BP	0.50	NIL	0.153
4.	Empty Gelatin Capsules size "2" Red/ White Signature Printed	-	BP	1 Nos.	1 %	309060
Average Fill Weight = 307 mg						

3. Pharmaceutical form

Hard Gelatin Capsule

Red/white coloured cap & body, hard gelatin signature printed capsules of size "2" containing white powder.

4. Clinical particulars

4.1 Therapeutic indications

Epilepsy

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

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.

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
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 3600mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300mg/day increments every 2-3 days up to a maximum dose of 3600mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800mg/day is one week, to reach 2400mg/day is a total of 2 weeks, and to reach 3600mg/day is a total of 3 weeks.

Dosages up to 4800mg/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 15mg/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 35mg/kg/day. Dosages up to 50mg/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 900mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300mg/day increments every 2-3 days up to a maximum dose of 3600mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800mg/day is one week, to reach 2400mg/day is a total of 2 weeks, and to reach 3600mg/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 capsules can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2

DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION

Creatinine Clearance (ml/min)	Total Daily Dosea (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150b -600
<15c	150b -300

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

b The 150mg daily dose to be administered as 300mg every other day.

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

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg, then 200 to 300mg 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 300mg 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).

4.3Contraindications

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

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 .

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.

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 anticonvulsants 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 post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

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.

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.

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.

Excipients with known effect

Gabapentin Accord-UK capsules contain lactose

Patients with rare hereditary problems of galactose intolerance, the total lactase 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 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 and 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 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 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 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 practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely.

It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

Gabapentin crosses the human placenta.

There are no or limited amount of 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 causally 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 (> 1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10,000; <1/1,000); very rare (<1/10,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from the 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.

System organ class	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), 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	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
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, 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
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, 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.

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses 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. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses. Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is 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 8000mg/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 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 α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ 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 α2δ 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 centres 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 (≥ 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 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 and 20µg/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	300mg (N = 7)		400mg (N = 14)		800mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
Cmax (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
tmax (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% (%)	NA	NA	47.2	(25)	34.4	(37)

Cmax = Maximum steady state plasma concentration
tmax = Time for Cmax
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 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 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 2000mg/kg/day and to rats at 250, 1000, and 2000mg/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 2000mg/kg/day are 10 times higher than plasma concentrations in humans given 3600mg/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 2000mg/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 3600mg, (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 hind limbs in rodents, indicative of foetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000mg/kg/day during organogenesis and in rats given 2000mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600mg on a mg/m2 basis.

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

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000mg/kg/day in a fertility and general reproduction study, 1500mg/kg/day in a teratology study, and 500, 1000, and 2000mg/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.

There are some reports of neurodegenerative changes in the brains of offspring exposed to gabapentin during pregnancy from rodent studies published in the open literature. However, limitations in study

designs means the toxicological significance and clinical relevance of these findings are unclear. A GLP compliant perinatal and postnatal study in rats showed reversible behavioural changes in offspring exposed to 1000 mg/kg gabapentin (approximately 1 to 5 times the human does of 3600 mg on a mg/m2 basis) from GD15 to PND21. Overall, the available data is insufficient to determine the developmental neurotoxic potential of gabapentin.

In a teratology study in rabbits, an increased incidence of post-implantation foetal loss, occurred in pregnant rabbits given 60, 300, and 1500mg/kg/day during organogenesis. These doses are approximately 0.3 to 8 times the daily human dose of 3600mg on a mg/m2 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

Sodium Starch Glycolate BP

Magnesium Stearate BP

Colloidal Anhydrous Silica BP

Empty Gelatin Capsules size “2” Red/ White Signature printed

6.2 Incompatibilities

None known.

6.3 Shelf Life

30 months

6.4 Special precautions for storage

Store below 30°C in a cool & dry place. Protect from light.

6.3 Nature and contents of container

10 x 10 Capsules Blister pack along with leaflet in one carton.

6.4 Special precautions for disposal and other handling

None stated.

PRODUCT NAME	**GABAPENTIN CAPSULES**
GENERIC NAME	**Gabapentin Capsules USP 300 mg**

7.0 Manufactured by

Hab Pharmaceuticals & Research Ltd.,

10, Pharmacity, Selaqui, Dehradun,

Uttarakhand - 248011, India

8.0 Marketing authorisation holder

Hab Pharmaceuticals & Research Ltd.,

10, Pharmacity, Selaqui,

Dehradun, Uttarakhand

- 248011, India