Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gabapentin Teva 300 mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active
Each capsule contains gabapentin 300mg

Excipients
Each capsule contains soya lecithin 0.0015mg
Each capsule contains Yellow Orange S (E110) 0.537mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Orange / Orange, size 0, hard gelatin capsule containing white to off-white powder. The capsule shells are printed with ’93’ and ‘39’.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Neuropathic Pain
Gabapentin is indicated for the treatment of neuropathic pain.

Epilepsy

Monotherapy in adults and children over 12 years of age
Gabapentin is used as an antiepileptic indicated for monotherapy or add-on treatment for adults and children over 12 years of age with partial seizures or partial seizures with secondary generalisation, including patients with newly diagnosed seizures.

Monotherapy in children under 12 years of age is not recommended until further information is available from controlled trials in this particular age group.

Add-on therapy in adults and children age 3 years and above
Gabapentin is used as an antiepileptic indicated for add-on treatment for partial seizures or partial seizures with secondary generalisation in adults and children age 3 years and above.

For children aged 3 years and above, Gabapentin should be initiated and supervised by a neurological specialist.

4.2 Posology and method of administration

Gabapentin Tevais given orally with or without food.

When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution with an alternative medication, this should be done gradually over a minimum of one week.

Neuropathic Pain

Adults (over the age of 18)
The starting dose is 900 mg per day given in three divided doses, and titrated if necessary, based on response, up to a maximum dose of 3600 mg per day. Therapy should be initiated by titrating the dose as described in Table 1.

Table 1: Dosing Chart – Initial Titration

Dose	Day 1	Day 2	Day 3
900mg	300mg Qd[a]	300mg BID[b]	300mg TID[c]

[a]QD = once a day [b]BID = two times a day [c]TID = three times a day

Elderly
Eldery patients may require dosage adjustment because of declining renal function with age (see Table 2).

Dosage Adjustment for Patients with Compromised Renal Function
Dosage adjustment is recommended in patients compromised renal function, as described in Table 2.

Table 2: Maintenance dosage of gabapentin in adults with reduced renal function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day Range [a]
≥80	900-3600 mg
50-79	600-1800 mg
30-49	300-900 mg
15-29	150[b]-600 mg
<15	150[b]-300 mg

[a] Total daily dose should be administered three times daily.
[b] To be administered as 300mg every other day.

Dosage adjustment for Patients on Haemodialysis
For patients undergoing haemodialysis who have never received gabpentin, a loading dose of 300 to 400mg is recommended then 200 to 300mg of gabapentin following each 4 hours of haemodialysis.

Epilepsy

Adults and Children (aged over 12 years of age)
The effective dose of Gabapentin is 900-3600mg/day.

The usual starting dose of Gabapentin as monotherapy for newly diagnosed patients is 900mg/day.

It is not necessary to monitor Gabapentin plasma concentrations to optimise Gabapentin Tevatherapy.

Titration to an effective dose can progress rapidly and can be achieved over a few days by administering 300mg once a day on Day 1, 300mg twice a day on Day 2 and 300mg three times a day on Day 3, as described in Table 1.Afterwards, the dose can be increased using increments of 300mg per day given in three equally divided doses to a maximum of 3600mg per day.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin Tevamay be given orally with or without food.

If Gabapentin Teva is discontinued and/or alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

Elderly
Elderly patients may need dosage adjustment due to decline of renal function. (see Table 2)

Children (3-12 years of age)
The starting dose of Gabapentin is 10 to 15 mg/kg/day given in divided doses (3 times a day). Titration to an affective dose can take place over 3 days. The effective dose of Gabapentin in paediatric patients age 5 years and older is 25 to 35 mg/kg/day in equally divided doses (3 times a day). The effective dose in paediatric patients aged 3 to less than 5 years is 40mg/kg/day given in equally divided doses (3 times a day). In long-term clinical study, dosages up to 50mg/kg/day have been well tolerated. The maximum time interval between doses should not exceed 12 hrs.

There was insufficient evidence available from appropriate studies upon which to base dosage recommendations for monotherapy use in children under the age of 12 years.

Patients with Compromised Renal function
It is recommended that patients with compromised renal function have their dosage adjusted (see Table 2).

Patients on Haemodialysis
For patients undergoing haemodialysis who have never received Gabapentin, a loading dose of 300mg to 400mg is recommended, then 200 to 300 mg Gabapentin following each 4 hours of haemodialysis.

4.3 Contraindications

Gabapentin Teva is contra-indicated in patients who have shown hypersensitivity to any of the constituents including soya oil.

4.4 Special warnings and precautions for use

Abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus although, to date, there have been no reported cases of rebound seizures with gabapentin. (see section 4.2, Posology and method of administration). Dose reduction, discontinuation or substitution of alternative anticonvulsant medication should be done gradually over a minimum of one week at the discretion of the clinician.

Generally, gabapentin is not considered effective in the treatment of absence seizures.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (See section 4.5, Interaction with other medicinal products and other forms of interactions).

Patients with epilepsy can be the subject of mood and behavioural disturbances. Although these have been noted in patients on gabapentin, a causal link has not been established.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptics 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 ideations 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 ideations 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 behaviour emerge.

4.5 Interaction with other medicinal products and other forms of interaction

Morphine: 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 gababpentin AUC increased by 44% compared to

gabapentin administered without morphine. This was associated with an increased pain threshold (cold pressor test). The clinical significance of such changes has not been defined. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The observed opioid-mediated side effects associated with morphine plus gabapentin did not differ significantly from morphine plus placebo. The magnitude of interaction at other doses is not known. (*see section 4.4, Special warnings and precautions for use*).

Gabapentin Tevamay 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.

No interaction was observed between gabapentin and phenytoin, valproic acid, carbamazepine or Phenobarbital. Steady-state pharmacokinetics of gabapentin are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

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

Co-administration of antacids containing aluminium and magnesium reduces the bioavailability of gabapentin up to 24%. It is recommended that gabapentin is taken about two hours after any administration of antacid.

Renal excretion of gabapentin is not altered by probenecid. A slight decrease in renal excretion of gabapentin, that is observed when co-administration with cimetidine, is of no significant clinical importance. Food does not alter the pharmacokinetics of gabapentin.

False positive readings were reported with the Ames N-Multistix SG dipstick test when gabapentin or placebo were added to other anticonvulsant drugs. In this case, the more specific sulphosalicylic acid precipitation method is recommended to determine urinary protein.

4.6 Fertility, pregnancy and lactation

The safe use of gabapentin in human pregnancy has not been established. Reproduction studies in mice at doses up to 42 times, in rats at doses up to 28 times and in rabbits at doses up to 21 times the human dose have shown no cases of impaired fertility or harm to the foetus. However, as animal reproduction studies are not always predictive of human response, administration of gabapentin should only be recommended in pregnancy if clearly needed.

Gabapentin is excreted in human milk but the effect on the nursing infant is unknown. However as many drugs are excreted in human milk, there can be potential for serious adverse reactions from gabapentin in nursing infants. A decision should therefore be made to either discontinue nursing or to discontinue the drug, taking into account the importance of gabapentin to the mother.

4.7 Effects on ability to drive and use machines

Like all anticonvulsants, the mode of action of gabapentin is on the central nervous system. Drowsiness, dizziness, or other related symptoms may occur upon administration of gabapentin. These incidents, although mild or moderate, may be dangerous in patients driving or operating machinery, particularly until when the individual patients experience with the drug is established.

4.8 Undesirable effects

Neuropathic Pain
Table 34 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients with Neuropathic pain in studies comparing gabapentin with placebo.

Table 34 – Summary of Treatment Emergent Signs and Symptoms in ≥1% of Gabapentin-Treated Patients in Neuropathic Pain Placebo-Controlled Studies

COSTART Body System/Adverse Event	Gabapentin N=821 N of Pts (%)		Placebo N=537 N of Pts (%)	
Body as a Whole				
Abdominal Pain	23	(2.8)	17	(3.2)
Accidental Injury	32	(3.9)	17	(3.2)
Asthenia	41	(5.0)	25	(4.7)
Back Pain	19	(2.3)	8	(1.5)
Flu Syndrome	21	(2.6)	14	(2.6)
Headache	45	(5.5)	33	(6.1)
Infection	38	(4.6)	40	(7.4)
Pain	30	(3.7)	36	(6.7)
Digestive System				
Constipation	19	(2.3)	9	(1.7)
Diarrhoea	46	(5.6)	24	(4.5)
Dry Mouth	27	(3.3)	5	(0.9)
Dyspepsia	16	1.9)	10	(1.9)
Flatulence	14	(1.7)	6	(1.1)
Nausea	45	(5.5)	29	(5.4)
Vomiting	16	(1.9)	13	(2.4)
Metabolic and Nutritional				
Peripheral Oedema	44	(5.4)	14	(2.6)
Weight Gain	14	(1.7)	0	(0.0)
Nervous System				
Abnormal Gait	9	(1.1)	0	(0.0)
Amnesia	15	(1.8)	3	(0.6)
Ataxia	19	(2.3)	0	(0.0)
Confusion	15	(1.8)	5	(0.9)
Dizziness	173	(21.1)	35	(6.5)
Hypaesthesia	11	(1.3)	3	(0.6)
Somnolence	132	(16.1)	27	(5.0)
Thinking Abnormal	12	(1.5)	0	(0.0)
Tremor	9	(1.1)	6	(1.1)
Vertigo	8	(1.0)	2	(0.4)
Respiratory System				
Dyspnoea	9	(1.1)	3	(0.6)
Pharyngitis	15	(1.8)	7	(1.3)
Skin Appendages				
Rash	14	(1.7)	4	(0.7)
Special Senses				
Amblyopia	15	(1.8)	2	(0.4)

Epilepsy

Gabapentin has been evaluated for safety in more than 2000 patients and was well tolerated.

Incidence in Add-on Controlled Clinical Trials

Table 4 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients with partial seizures during 12-week controlled studies comparing gabapentin with placebo. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy.

Adverse events, obtained from pooled data from five multicentre studies, were usually reported as mild to moderate (66% of patients) with a median time to resolution of two weeks.

Table 4: Summary of Treatment Emergent Signs and Symptoms in ≥1% of Gabapentin Treated Patients in Add-On Therapy Placebo-Controlled Studies

COSTART Body system/Adverse Event	Gabapentin [a] N=543		Placebo[a] N=378	
	N of pts	(%)	N of Pts	(%)
Body as Whole				
Abdominal Pain	10	1.8	9	2.4
Back Pain	10	1.8	2	0.5
Fatigue	60	11.0	19	5.0
Fever	7	1.3	5	1.3
Headache	44	8.1	34	9.0
Viral Infection	7	1.3	8	2.1
Cardiovascular				
Vasodilation	6	1.1	1	0.3
Digestive System				
Constipation	8	1.5	3	0.8
Dental abnormalities	8	1.5	1	0.3
Diarrhoea	7	1.3	8	2.1
Dyspepsia	12	2.2	2	0.5
Increased appetite	6	1.1	3	0.8
Mouth or Throat Dry	9	1.7	2	0.5
Nausea and/or vomiting	33	6.1	27	7.1
Haematologic & Lymphatic				
Leucopoenia	6	1.1	2	0.5
WBC Decreased	6	1.1	2	0.5

COSTART Body system/Adverse Event	Gabapentin[a] N=543		Placebo[a] N=378	
Metabolic and Nutritional				
Peripheral Oedema	9	1.7	2	0.5
Weight Increase	16	2.9	6	1.6
Musculoskeletal system				
Fracture	6	1.1	3	0.8
Myalgia	11	2.0	7	1.9
Nervous system				
Amnesia	12	2.2	0	0.0
Ataxia	68	12.5	21	5.6
Confusion	9	1.7	7	1.9
Coordination Abnormal	6	1.1	1	0.3
Depression	10	1.8	7	1.8
Dizziness	93	17.1	26	6.9
Dysarthria	13	2.4	2	0.5
Emotional Lability	6	1.1	5	1.3
Insomnia	6	1.1	7	1.9
Nervousness	13	2.4	7	1.9
Nystagmus	45	8.3	15	4.0
Somnolence	105	19.3	33	8.7
Think abnormal	9	1.7	5	1.3
Tremor	37	6.8	12	3.2
Twitching	7	1.3	2	0.5
Respiratory system				
Coughing	10	1.8	5	1.3
Pharyngitis	15	2.8	6	1.3
Rhinitis	22	4.1	14	3.7

COSTART Body system/Adverse Event	Gabapentin[a] N=543		Placebo[a] N=378	
Skin and appendages				
Abrasion	7	1.3	0	0.0
Acne	6	1.1	5	1.3
Pruritis	7	1.3	2	0.5
Rash	8	1.5	6	1.6
Special sense				
Amblyopia	23	4.2	4	1.1
Diplopia	32	5.9	7	1.9
Urogenital system				
Impotence	8	1.5	4	1.1

Other Adverse Events Observed During All Add-on Clinical Trials

Those events that occurred in at least 1% of the study participants with epilepsy who received gabapentin as add-on therapy in any clinical study and that are not described in the previous section are summarised below.

Body As A Whole: asthenia, malaise, facial oedema

Cardiovascular system: hypertension

Digestive System: flatulence, anorexia, gingivitis

Haemic and Lymphatic Systems: purpura most often described as bruises resulting from physical trauma

Musculoskeletal System: arthralgia

Nervous System: vertigo, hyperkinesia, increased, decreased or absent reflexes, paraesthesia, anxiety, hostility

Respiratory System: pneumonia

Urogenital System: urinary tract infection

Special Senses: abnormal vision most often described as a visual disturbance

The side effect reported in dose controlled monotherapy studies was similar to that in add-on studies.

Post-marketing surveillance

As with the other antiepileptic drugs, there have been rare reports of pancreatitis, elevated liver function tests (LFT's), erythema multiforme, acute kidney failure, allergic reaction including urticaria, alopecia, angioedema, blood glucose fluctuations in patients with diabetes, chest pain, hallucinations, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, tinnitus, urinary incontinence, Stevens Johnson Syndrome and sudden unexplained deaths where a causal relationship to treatment has not been established

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

Children
Side effects that occurred in children aged 3-12 years, with an incidence of 2% or greater than placebo in controlled add-on trials, were: somnolence, fatigue, weight increase, hostility, emotional lability, dizziness, hyperkinesia, nausea/vomiting, viral infection, fever, bronchitis, respiratory infection. Some of these side effects may be attributed to common viral childhood illness.

4.9 Overdose

In limited experience with overdoses, the following have been noted: dizziness, double vision, slurred speech, drowiness, lethargy and mild diarrhoea. Overdoses of Gabapentin, up to 49g ingested at one time, have been reported. All patients recovered fully with supportive care. Therefore, acute, life-threatening toxicity has not been observed with Gabapentin overdose of up to 49g per day. Reduced absorption of Gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, toxicity from overdose.

Although Gabapentin can be removed by haemodialysis it is not usually required. However, in patients with renal impairment, haemodialysis may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Gabapentin is an anticonvulsant 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.

The identification and function of the gabapentin binding site remains to be elucidated and the significance of its various actions to the anticonvulsant effect remains to be established.

Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

5.2 Pharmacokinetic properties

Following single oral doses of Gabapentin, regardless of dose size or formulation, the mean plasma gabapentin concentrations (Cmax) occurred approximately 3 hours (Tmax). Following multiple dose administration the mean Tmax values were approximately 1 hour shorter than the values following single-dose administration.

At doses of 300-4800mg, mean Cmax and AUC values increased with increasing dose, however, the increase was less than dose proportional.

Following repeated Gabapentin administration, steady-state was achieved within 1 to 2 days after the start of the multiple dosing and was maintained throughout the dosing regime.

Following single-dose administrations of 300 and 400mg of gabapentin, the plasma gabapentin concentration-time profiles were similar between gabapentin solution and capsule formulations. Absolute bioavailability of a 300mg oral dose of Gabapentin was approximately 60%. Following multiple-dose administration at doses of 300mg and 400mg, Gabapentin bioavailability was unchanged.
The presence of food did not affect the bioavailabitly of Gabapentin.

Gabapentin is not metabolised in humans and does not induce hepatic mixed function oxidase enzymes.

Gabapentin elimination from plasma following IV administration was best described by linear pharmacokinetics. Elimination half-life (T½) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters, apparent plasma T½ and renal clearance (CL_R) were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. Since gabapentin is not metabolised in humans, the amount of drug recovered in urine is indicative of gabapentin bioavailability. Following a single 200mg oral dose of [C_{14}] gabapentin, recovery of radioactivity was essentially complete with approximately 80% and 20% of the dose recovered in urine and faeces, respectively.

As renal function (which was determined by creatinine clearance) decreases with increasing age, gabapentin oral clearance, renal clearance and elimination-rate constant decrease proportionally.
Gabapentin pharmacokinetics was determined in 24 healthy paediatric subjects between the ages of 4 and 12 years. In general, pharmacokinetic parameters were comparable to those in adults.

5.3 Preclinical safety data

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 the therapeutic concentrations in humans given the recommended maximum therapeutic dose of 3600mg/day.

The pancreatic acinar cell tumours in male rats were 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.

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of metabolic activation. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talc
Pregelatinised maize starch

Capsule shell consists of:
Gelatin
Erythrosin (E172)
Yellow orange S (E110)
Titanium dioxide (E171)

Capsule ink contains:
Shellac
Black iron oxide (E172)
Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.
Keep blister in the outer carton.

6.5 Nature and contents of container

Transparent or white opaque PVdC coated PVC/ Aluminium foil blister strips in pack sizes of 20, 30, 50, 84, 100 and 500 tablets. Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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