Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gabapentin Teva 800 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 800 mg film-coated tablet contains 800 mg of gabapentin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off-white, oval shaped, bevelled edged, film-coated tablet.
On one side engraved “7174”, and on the other side engraved “93”.

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

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).

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 l	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg three times a day

Discontinuation of gabapentin
In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Epilepsy

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.

Adults and adolescents:
In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and. tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

Children aged 6 years and above:
The starting dose should range from l0 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 3600mg/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 l00mg 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 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/lmin).

[b] To be administered as 300 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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

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 antiepileptics, attempts to withdraw concomitant antiepileptics in treatment refractory patients on more than one antiepileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

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.

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.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of antiepileptic 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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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, and the dose of gabapentin or morphine 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.

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

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.

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.

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 to <1/10), uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (< 1/10,000) including isolated reports, not known (cannot be estimated from the available data). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported. Additional reactions reported from post−marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 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

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 paraesthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon: hypokinesia
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 symptoms(see section 4.4)*

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia, back pain, twitching
Not known: *myoclonus*

Renal and urinary disorders
Not known: *acute renal failure, incontinence*

Reproductive system and breast disorders
Common: impotence
Not known: *breast hypertrophy, gynaecomastia*

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 glucose fluctuations in patients with diabetes*

Injury, poisoning and procedural complications
Common: accidental injury, fracture, abrasion

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 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, 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 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Other antiepileptics ATC code: NO3AX12

The precise mechanism of action of gabapentin is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the $alpha_2$-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100 μM, which are not achieved *in vivo.* Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro.* Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

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 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 μg/ml and 20 μg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3
Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N =7)		400 mg (N = 14)		800 mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{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%(%)	NA	NA	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-lime curve from lime 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.

Metabolism

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.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T 1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m^2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m^2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 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 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 1/4 to 8 times the daily human dose of 3600 mg on a mg/m^2 basis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone K30
Cellulose, microcrystalline
Crospovidone
Talc
Hydrogenated vegetable (cotton) oil Type I

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C.
Bottles: Keep the bottle tightly closed, store in the original package
Blisters: Store in the original package, keep blister in the outer carton

6.5 Nature and contents of container

Bottle
White, round HDPE bottle with metal cap with polyethylene liner and polystyrene pressure foam seal. The bottle contains a cylinder (with silica gel as desiccant).

Pack sizes: one bottle containing 1, 20, 30, 45, 50, 84, 90, 100, 200 or 500 film-coated tablets

Blisters
1. PVC-PE-PVdC-PE-PVC/aluminium blister
2. PVC-PE-PVdC/aluminium blister
3. aluminium/ aluminium blister
Pack sizes 1, 20, 30, 45, 50, 84, 90, 100, 200 or 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10,
3542 DR Utrecht,
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/55/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th September 2008

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10 DATE OF REVISION OF THE TEXT

April 2013