



Public Assessment Report
from the Norwegian Medicines Agency

Cenesid capsules, hard 100 mg
Cenesid capsules, hard 300 mg
Cenesid capsules, hard 400 mg
gabapentin

MA-holder: Teva Sweden AB, Sweden

MA-numbers in Norway: 07-4977, 07-4978 and 07-4979

Date: 2008-07-15

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

- Module 1: Information about the initial procedure
- Module 2: Summary of product Characteristics (SPC)
- Module 3: Package Leaflet
- Module 4: Labelling
- Module 5: Scientific discussion

Module 1: Information about the initial procedure:

1. Type of application: Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic application, claiming essential similarity
2. Active substance: gabapentin
3. Pharmaceutical form: capsules, hard
4. Strength: 100, 300 and 400 mg
5. MA holder: Teva Sweden AB, Helsingborg, Sweden
6. Reference Member State: Norway
7. Concerned Member States: Austria, Belgium, Denmark, Greece, Ireland, Luxembourg and Slovenia
8. Procedure-number: : NO/H/0130/001-003/DC
9. Timetable:
Start (Day 0): 11.06.2007
End (Day 196): 15.04.2008

Module 2: Summary of product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

Cenesid 100 mg hard capsules
Cenesid 300 mg hard capsules
Cenesid 400 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg capsule contains 100 mg of gabapentin
Each 300 mg capsule contains 300 mg of gabapentin
Each 400 mg capsule contains 400 mg of gabapentin

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

100 mg Capsule, hard

Hard gelatine capsule with a grey cap and body, filled with white to off-white powder with small agglomerates.

The capsule cap and body are each imprinted with the numbers '93' and '38'.

300 mg Capsule, hard

Hard gelatine capsule with an orange cap and body, filled with white to off-white powder with small agglomerates.

The capsule cap and body are each imprinted with the numbers '93' and '39'.

400 mg Capsule, hard

Hard gelatin capsule with a brown cap and body, filled with a white to off-white powder with small agglomerates.

The capsule cap and body are each imprinted with the numbers '93' and '40'.

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

Epilepsy

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

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 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 100mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

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/min).

^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 anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractory 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.

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.

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.

300 mg: Contains sunset yellow (E110) which may rarely cause allergic reactions.

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 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $\leq 1/100$) and rare ($\geq 1/10,000$; $\leq 1/1,000$). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

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

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

Rare: thrombocytopenia

Immune system disorders

Rare: allergic reactions (e.g. urticaria)

Metabolism and Nutrition Disorders

Common: anorexia, increased appetite

Psychiatric disorders

Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal

Rare: 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

Rare: movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders

Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders

Common: vertigo

Rare: tinnitus

Cardiac disorders

Rare: palpitations

Vascular disorder

Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders

Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence

Rare: pancreatitis

Hepatobiliary disorders

Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders

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

Rare: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia, myalgia, back pain, twitching

Renal and urinary disorders

Common: incontinence

Rare: acute renal failure

Reproductive system and breast disorders

Common: impotence

General disorders and administration site conditions

Very Common: fatigue, fever

Common: peripheral or generalized oedema, abnormal gait, asthenia, pain, malaise, flu syndrome

Rare: 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

Rare: Blood glucose fluctuations in patients with diabetes, elevated liver function tests

Injury and poisoning

Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

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.

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 α_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 μ M, 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 (\geq 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
<6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5 144

*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-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.

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/m² of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m² basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 on a mg/m² basis.

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

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

of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m² basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m² basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Talc

Pregelatinised maizestarch

Capsule cap / body:

Gelatin

Titanium dioxide (E171)

In addition: 100 mg capsules contain black iron oxide (E172)

In addition: 300 mg capsules contain erythrosin (E127), sunset yellow (E110)

In addition: 400 mg capsules contain black iron oxide (E172), red iron oxide (E172)
yellow iron oxide (E172)

Printing ink:

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 container. Keep blister in the outer carton.

6.5 Nature and contents of container

Transparent or white opaque PVC/PVdC-aluminium blisters.

Pack sizes 100 mg: 1, 20 30, 50, 84, 100, 200 or 500 capsules, hard.

Pack sizes 300 mg: 1, 20, 30, 50, 84, 100, 200 or 500 capsules, hard.

Pack sizes 400 mg: 1, 20, 30, 50, 84, 100, 200 or 500 capsules, hard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Sweden AB
PO Box 1070
251 10 Helsingborg
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

2008-04-15

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cenesid 100 mg hard capsules
Cenesid 300 mg hard capsules
Cenesid 400 mg hard capsules

Gabapentin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cenesid is and what it is used for
2. Before you take Cenesid
3. How to take Cenesid
4. Possible side effects
5. How to store Cenesid
6. Further information

1. WHAT CENESID IS AND WHAT IT IS USED FOR

Cenesid belongs to a group of medicines used to treat epilepsy and peripheral neuropathic pain.

Epilepsy: Cenesid is used to treat various forms of epilepsy (seizures that are initially limited to certain parts of the brain, whether the seizure spreads to other parts of the brain or not). Your doctor will prescribe Cenesid for you to help treat your epilepsy when your current treatment is not fully controlling your condition. You should take Cenesid in addition to your current treatment unless told otherwise. Cenesid can also be used on its own to treat adults and children over 12 years of age.

Peripheral neuropathic pain: Cenesid is used to treat long lasting pain caused by damage to the nerves. A variety of different diseases can cause peripheral (primarily occurring in the legs and/or arms) neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles etc.

2. BEFORE YOU TAKE CENESID

Do not take Cenesid

- if you are allergic (hypersensitive) to gabapentin (if you develop a rash or other signs of allergy (hypersensitivity)).
- if you are allergic (hypersensitive) to one or more of the other ingredients of Cenesid. These other ingredients are mentioned in section '6. Further information' of this leaflet. Allergic reactions can be identified for example by the appearance of a rash, itching, or a swollen face.

Take special care with Cenesid

- if you suffer from kidney problems
- if you develop signs such as persistent stomach pain, feeling sick and being sick

contact your doctor immediately.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription

If you are taking any medicines containing morphine, please tell your doctor or pharmacist as morphine may increase the effect of Cenesid.

Cenesid is not expected to interact with other antiepileptic drugs or the oral contraceptive pill.

Cenesid may interfere with some laboratory tests, if you require a urine test tell your doctor or hospital that you are taking Cenesid.

If Cenesid and antacids containing aluminium and magnesium are taken at the same time, absorption of Cenesid from the stomach may be reduced. It is therefore recommended that Cenesid is taken at the earliest two hours after taking an antacid.

Taking Cenesid with food and drink
Cenesid can be taken with or without food.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Cenesid should not be taken during pregnancy, unless you are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential.

There have been no studies specifically looking at the use of gabapentin in pregnant women, but other medications used to treat seizures have reported an increased risk of harm to the foetus, particularly when more than one seizure medication is taken at the same time. Therefore, whenever possible and only under the advice of your doctor, you should try to take only one seizure medication during pregnancy.

Do not suddenly discontinue taking this medicine as this may lead to breakthrough seizure, which could have serious consequences for you and your baby.

Contact your doctor immediately if you become pregnant, think you might be pregnant or are planning to become pregnant while taking Cenesid.

Gabapentin, the active substance of Cenesid, is excreted in human milk. Because the effect on the nursing infant is unknown, it is not recommended to breast-feed your baby while using Cenesid.

Driving and using machines

Cenesid may produce dizziness, drowsiness and tiredness. You should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medication affects your ability to perform these activities.

Important information about some of the ingredients of Cenesid

The 300 mg capsules contain sunset yellow (E110) which may cause rarely allergic reactions.

3. HOW TO TAKE CENESID

Always take Cenesid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will determine what dose is appropriate for you.

If you have the impression that the effect of Cenesid is too strong or too weak, talk to your doctor or pharmacist.

If you are an elderly patient (over 65 years of age), you should take Cenesid normally except if you have problems with your kidneys.

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.

Always swallow the capsules whole with plenty of water.

Continue taking Cenesid until your doctor tells you to stop.

Peripheral Neuropathic Pain:

Take the number of capsules as instructed by your doctor. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased stepwise up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 divided doses, i.e. once in the morning, once in the afternoon and once in the evening.

Epilepsy:

Adults and adolescents:

Take the number of capsules as instructed. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased stepwise up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 divided doses, i.e. once in the morning, once in the afternoon and once in the evening.

Children aged 6 years and above:

The dose to be given to your child will be decided by your doctor as it is calculated against your child's weight. The treatment is started with a low initial dose which is gradually increased over a period of approximately 3 days. The usual dose to control epilepsy is 25-35 mg/kg/day. It is usually given in 3 divided doses, by taking the capsule(s) or tablet(s) each day, usually once in the morning, once in the afternoon and once in the evening.

Cenesid is not recommended for use in children below 6 years of age.

If you take more Cenesid than you should

Call your doctor or go to the nearest hospital emergency unit immediately. Take along any capsules that are left, the container and the label so that the hospital can easily tell what medicine you have taken

If you forget to take Cenesid

If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Cenesid

Do not stop taking Cenesid unless your doctor tells you to. If your treatment is stopped it

should be done gradually over a minimum of 1 week. If you stop taking Cenesid suddenly or before your doctor tells you, there is an increased risk of seizures.

If you have any further questions on the use of his product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cenesid can cause side effects, although not everybody gets them.

Very common side-effects which may affect more than 1 person in 10 are listed below:

- Viral infection
- Feeling drowsy, dizziness, lack of coordination
- Feeling tired, fever

Common side-effects which may affect more than 1 person in 100 are listed below:

- Pneumonia, respiratory infection, urinary tract infection, infection, inflammation of the ear
- Low white blood cell counts
- Anorexia, increased appetite
- Anger towards others, confusion, fluctuation in mood, depression, anxiety, nervousness, difficulty with thinking
- Convulsions, jerky movements, difficulty with speaking, loss of memory, tremor, difficulty sleeping, headache, sensitive skin, decreased sensation, difficulty with coordination, unusual eye movement, increased, decreased or absent reflexes
- Blurred vision, double vision
- Vertigo
- High blood pressure, flushing or dilation of blood vessels
- Difficulty breathing, bronchitis, sore throat, cough, dry nose
- Vomiting (being sick), nausea (feeling sick), problems with teeth, inflamed gums, diarrhoea, stomach pain, indigestion, constipation, dry mouth or throat, flatulence
- Facial swelling, bruises, rash, itch, acne
- Joint pain, muscle pain, back pain, twitching
- Incontinence
- Difficulties with erection
- Swelling in the legs and arms or swelling that may involve the face, trunk and limbs, difficulty with walking, weakness, pain, feeling unwell, flu-like symptoms
- Decrease in white blood cells, increase in weight
- Accidental injury, fracture, abrasion

Rare side-effects which may affect less than 1 person in 1000 are listed below:

- Decreased platelets (blood clotting cells)
- Allergic reaction such as hives
- Hallucinations
- Problems with abnormal movements such as writhing, jerking movements and stiffness
- Ringing in the ears
- Racing heartbeat
- Inflammation of the pancreas
- Inflammation of the liver, yellowing of the skin and eyes
- Severe skin reactions that require immediate medical attention, swelling of the lips and face, skin rash and redness, hair loss
- Acute kidney failure
- Adverse events following the abrupt discontinuation of Cenesid (anxiety, difficulty sleeping, feeling sick, pain, sweating), chest pain
- Blood glucose fluctuations in patients with diabetes, abnormal blood test results suggesting problems with the liver.

Additionally in clinical studies in children, aggressive behaviour and jerky movements were reported commonly.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CENESID

Keep out of the reach and sight of children.

Do not use Cenesid after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cenesid contains

— The active substance is gabapentin. Each hard capsule contains either 100 mg, 300 mg or 400 mg gabapentin.

The other ingredients are:

in 100 mg

Capsules: talc, pregelatinised (maize) starch

Capsule cap / body: gelatin, black iron oxide (E172), titanium dioxide (E171)

Printing ink: shellac, black iron oxide (E172), propylene glycol

in 300 mg

Capsules: talc, pregelatinised (maize) starch

Capsule cap / body: gelatin, erythrosin (E127), sunset yellow (E110), titanium dioxide (E171)

Printing ink: shellac, black iron oxide (E172), propylene glycol

in 400 mg

Capsules: talc, pregelatinised (maize) starch

Capsule cap / body: gelatine, black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171)

Printing ink: shellac, black iron oxide (E172), propylene glycol

What Cenesid looks like and contents of the pack

100 mg Capsule, hard

Hard gelatin capsule with a grey cap and body, filled with a white to off-white powder with small agglomerates. The capsule cap and body are each imprinted with the numbers '93' and '38'.

300 mg Capsule, hard

Hard gelatin capsule with an orange cap and body, filled with a white to off-white powder with small agglomerates. The capsule cap and body are each imprinted with the numbers '93' and '39'.

400 mg Capsule, hard

Hard gelatin capsule with a brown cap and body, filled with a white to off-white powder with small agglomerates. The capsule cap and body are each imprinted with the numbers '93' and '38'.

'40'.

Pack sizes 100 mg: 1, 20, 30, 50, 84, 100, 200 or 500 capsules, hard.

Pack sizes 300 mg: 1, 20, 30, 50, 84, 100, 200 or 500 capsules, hard.

Pack sizes 400 mg: 1, 20, 30, 50, 84, 100, 200 or 500 capsules, hard.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
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251 10 Helsingborg
Sweden

Manufacturers
Teva UK Ltd, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK
Teva Pharmaceutical Works Private Ltd Company, Pallagi út 13, H-4042 Debrecen
Teva Pharmaceutical Works Private Ltd Company, Táncsics Mihály út 82, H-2100 Gödöllo

This leaflet was last approved in 2008-04-15

Module 4: Labelling

Not included

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Cenesid capsules, hard 100, 300 and 400 mg “Teva”. The procedure was finalised at 2008-04-15. For information on changes after this date please refer to the Annex ‘Update’.

I. INTRODUCTION

Based on review of the submitted data, the Member States will grant a marketing authorisation (MA) for Cenesid capsules, hard 100, 300 and 400 mg from Teva. The first date of authorisation in Norway was 2008-07-15. The product is indicated for the following 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.

A comprehensive description of the indications and the posology is given in the SPC (see Module 3).

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application.

This concerns a generic application claiming essential similarity to the innovator product Neurontin “Pfizer”. Neurontin capsules, hard have been marketed in Norway since 1996-08-21. This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. This has been demonstrated for Cenesid capsules, hard. No new pre-clinical or further clinical studies were conducted, which is acceptable for this generic application.

II. QUALITY ASPECTS

II.1 Drug Substance

The chemical-pharmaceutical documentation in relation to Cenesid capsules are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

II.2 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 2 years with storage conditions below 25°C for the drug product is considered acceptable (further details on storage conditions are given in the SPC).

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of gabapentin are well known. As gabapentin is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and further studies are not required.

IV. CLINICAL ASPECTS

The pharmacodynamic properties and clinical efficacy and safety of gabapentin are well known. As gabapentin is a widely used, well-known active substance, the applicant has not provided additional clinical studies and further studies are not required. The clinical overview based on literature review is, thus, appropriate.

The submitted bioequivalence studies show that Cenesid capsules, hard, 100 mg and 400 mg are bioequivalent to Neurontin “Pfizer” capsules, hard, 100 mg and 400 mg, respectively, with respect to both rate and extent of absorption of gabapentin. The results of the submitted bioequivalence studies with the 100 mg and 400 mg formulation can be extrapolated to the 300 mg strength, according to conditions in *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* CPMP/EWP/QWP/1401/98, section 5.4.

An adequate review of published clinical data and the bioequivalence has been shown.

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Neurontin, marketed by Pfizer.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

Cenesid capsules, hard 100, 300 and 400 mg “Teva” is a generic medicinal product to Neurontin “Pfizer”. Neurontin is a well-known medicinal product with an established efficacy and safety profile.

The risk/benefit ratio is considered positive and Cenesid capsules, hard 100, 300 and 400 mg “Teva” is recommended for approval.