Generic Name Gabapentin 400mg + Nortriptyline 10mg

Trade Name Pentanerv-NT

1. NAME OF THE MEDICINAL PRODUCT: Gabapentin 400mg + Nortriptyline 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains:

Gabapentin USP……..400mg
Nortryptyline Hydrochloride IP……..10 mg

3. PHARMACEUTICAL FORM: Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Combination indicated for neuropathic pain

4.2 Posology and Method of Administration

Combination can be given as two-three times a day orally

4.3 **Contraindications**
Hypersensitivity to the active substance or to any of the excipients
Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
Severe liver disease.
Mania.
Nortriptyline is contraindicated for the nursing mother and for children under the age of six years

4.4 Special Warnings and Special Precautions for Use

Gabapentin

Suicidal ideation and behaviour

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.

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

Seizures
Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other antiepileptics, attempts to withdraw concomitant antiepileptics in treatment refractive 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.

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been postmarketing reports of confusion, loss of consciousness and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Concomitant use with opioids
Patients who require concomitant treatment with opioids should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or opioids should be reduced appropriately (see section 4.5).

Use in elderly patients (over 65 years of age)
No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

Paediatric population

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Abuse and Dependence

Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.

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.

Nortriptyline

Suicide/suicidal thoughts or clinical worsening. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or this exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy in early treatment and following dose changes. Patients (an caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Withdrawal symptoms, including insomnia, irritability and excessive perspiration, may occur on abrupt cessation of therapy.

The use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If administered to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge.

Cross sensitivity between nortriptyline and other tricyclic antidepressants is a possibility.

Patients with cardiovascular disease should be given nortriptyline only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia and strokes have occurred. Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

The use of nortriptyline should be avoided, if possible, in patients with a history of epilepsy. If it is used, however, the patients should be observed carefully at the beginning of treatment, for nortriptyline is known to lower the convulsive threshold.

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion and postural hypotension.

Troublesome hostility in a patient may be aroused by the use of nortriptyline.

Behavioural changes may occur in children receiving therapy for nocturnal enuresis.

If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy.

The possibility of a suicide attempt by a depressed patient remains after the initiation of treatment. This possibility should be considered in relation to the quantity of drug dispensed at any one time.

When it is essential, nortriptyline may be administered with electroconvulsive therapy, although the hazards may be increased.

Both elevation and lowering of blood sugar levels have been reported. Significant hypoglycaemia was reported in a Type II diabetic patient maintained on chlorpropamide (250mg/day), after the addition of nortriptyline (125mg/day).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Gabapentin

There are spontaneous and literature case reports of respiratory depression and/or sedation associated with gabapentin and opioid use. In some of these reports, the authors considered this a particular concern with the combination of gabapentin and opioids, especially in elderly patients.

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

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**.**

Nortriptyline

Drug interactions: Under no circumstances should nortriptyline be given concurrently with, or within two weeks of cessation of, therapy with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions and fatalities have occurred when similar tricyclic antidepressants were used in such combinations.
Nortriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.
Nortriptyline may decrease the antihypertensive effect of guanethidine, debrisoquine, bethanidine and possibly clonidine. Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.
Barbiturates may increase the rate of metabolism of nortriptyline.
Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the drug should be discontinued, if possible, for several days prior to the procedure, or the anaesthetist should be informed if the patient is still receiving therapy.
Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol.
The potentiating effect of excessive consumption of alcohol may lead to increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.
Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued.
Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 isoenzyme system, concomitant therapy with drugs also metabolised by this system may lead to drug interactions. Lower doses than are usually prescribed for either the tricyclic antidepressant or the other drug may therefore be required.
Greater than two-fold increases in previously stable plasma levels of nortriptyline have occurred when fluoxetine was administered concomitantly. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4 16 days for norfluoxetine).
Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (eg, quinidine), should be approached with caution.
Supervision and adjustment of dosage may be required when nortriptyline is used with other anticholinergic drugs.

4.6 Fertility, Pregnancy and Lactation

Gabapentin

Pregnancy
Risk related to epilepsy and antiepileptic medicinal products in general.
The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is 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.
Breast-feeding
Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Fertility
There is no effect on fertility in animal studies.

Nortriptyline

Pregnancy
The safety of nortriptyline for use during pregnancy has not been established, nor is there evidence from animal studies that it is free from hazard; therefore the drug should not be administered to pregnant patients or women of childbearing age unless the potential benefits clearly outweigh any potential risk.

Breast-feeding
Contraindicated for the nursing mother and for children under the age of six years.

4.7 Effects on Ability to Drive and Use Machines

Gabapentin

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.

Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore the patient should be warned accordingly.

4.8 Undesirable Effects

Gabapentin

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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.
Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body System	**Adverse drug reactions**
Infections and infestations	
Very Common	viral infection
Common	pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	
Common	leucopenia
Not known	*thrombocytopenia*
Immune system disorders	
Uncommon	allergic reactions (e.g. urticaria)
Not known	*hypersensitivity syndrome, a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms*
Metabolism and Nutrition Disorders	
Common	anorexia, increased appetite
Uncommon	hyperglycemia (most often observed in patients with diabetes)
Rare	hypoglycaemia (most often observed in patients with diabetes)
Not known	*hyponatraemia*
Psychiatric disorders	
Common	hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Not known	*hallucinations*
Nervous system disorders	
Very Common	somnolence, dizziness, ataxia
Common	convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	hypokinesia, mental impairment
Rare	loss of consciousness
Not known	*other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)*
Eye disorders	

Common	visual disturbances such as amblyopia, diplopia
Ear and Labyrinth disorders	
Common	vertigo
Not known	*tinnitus*
Cardiac disorders	
Uncommon	palpitations
Vascular disorders	
Common	hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Not known	*pancreatitis*
Hepatobiliary disorders	
Not known	*hepatitis, jaundice*
Skin and subcutaneous tissue disorders	
Common	facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	*Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)*
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	*rhabdomyolysis, myoclonus*
Renal and urinary disorder	
Not known	*acute renal failure, incontinence*
Reproductive system and breast disorders	
Common	impotence
Not known	*breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)*
General disorders and administration site conditions	
Very Common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalized oedema
Not known	*withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.*
Investigations	
Common	WBC (white blood cell count) decreased, weight gain
Uncommon	elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known	*blood creatine phosphokinase increased*
Injury and poisoning	
Common	accidental injury, fracture, abrasion
Uncommon	fall

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear

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.

Nortriptyline

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.
Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation

Neurological: Numbness, tingling, paraesthesia of extremities; inco ordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus.

Anticholinergic: Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Rash, petechiae, urticaria, itching, photosensitisation (avoid excessive exposure to sunlight); oedema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.
Haematological: Bone-marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia.

Gastro-intestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhoea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus.

Endocrine: Gynaecomastia in the male; breast enlargement and galactorrhoea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate secretion of antidiuretic hormone.

Other: Jaundice (simulating obstructive); altered liver function, hepatitis and liver necrosis; weight gain or loss; sweating; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Withdrawal symptoms: Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

Class Effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown.

4.9 Overdose

Gabapentin

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, loss of consciousness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise 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 not usually 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.

Nortriptyline

Signs and symptoms: 50mg of a tricyclic antidepressant can be an overdose in a child. Of patients who are alive at presentation, mortality of 0-15% has been reported. Symptoms may begin within several hours and may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, fever, rapid heart rate, decreased bowel sounds, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobinuric renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension and cardiac arrhythmias. Cardiac conduction may be slowed, with prolongation of QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmias (including Torsade de pointes and fibrillation) and death. Prolongation of QRS duration to more than 100msec is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilatation, central and peripheral alpha-adrenergic blockade and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient survived 5 hours of cardiac massage.

Treatment: Symptomatic and supportive therapy is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption.
Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate. Serum electrolytes should be monitored and managed. Refractory arrhythmias may respond to propranolol, bretylium or lignocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.
Seizures may respond to diazepam. Phenytoin may treat seizures and cardiac rhythm disturbances. Physostigmine may antagonise atrial tachycardia, gut immotility, myoclonic jerks and somnolence. The effects of physostigmine may be short-lived.
Diuresis and dialysis have little effect. Haemoperfusion is unproven. Monitoring should continue, at least until the QRS duration is normal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Gabapentin

Mechanism of action
Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug target other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the α2δ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centers through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

Nortriptyline

Nortriptyline is a tricyclic antidepressant with actions and uses similar to those of Amitriplyline. It is the principal active metabolite of Amitriplyline.
In the treatment of depression Nortriptyline is given by mouth as the hydrochloride in doses equivalent to Nortriptyline 10mg 3 or 4 times daily initially, gradually increased to 25mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10mg thrice daily. Inappropriately high plasma concentrations of Nortriptyline have been associated with deterioration in antidepressant response. Since Nortriptyline has prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

5.2 Pharmacokinetic Properties

Gabapentin

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 following Table

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)
$T_{1/2}$ (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC_{0-t} (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}
$T_{1/2}$ = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Biotransformation

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data

Nortriptyline

Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites). N-oxidation and conjugation with glucuronic acid. Nortriptyline is widely distributed throughout the body and is extensively bound to plasma and tissue protein. Plasma concentrations of Nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

5.3 Preclinical Safety Data

Gabapentin

Carcinogenesis
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasise or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is 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 mg 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/m2basis).

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/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.

Nortriptyline

There are no preclinical data of relevance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life:
2 yrs

6.2 Special Precautions for Storage:
Store in a cool and dry place. Protect from light

6.3 Nature and Contents of Container:
10's – blister
10 x 10's - carton

Marketed By:
Alkem Laboratories Limited,
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