SUMMARY OF PRODUCT CHARACTERISTICS

GABANORT-400 (Gabapentin 400 mg / Nortriptyline Hydrochloride 10 mg Film-Coated Tablets)

1. NAME OF THE MEDICINAL PRODUCT

GABANORT-400 (Gabapentin 400 mg / Nortriptyline Hydrochloride 10 mg Film-Coated Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains gabapentin 400 mg and nortriptyline hydrochloride 10 mg.

Excipients with known effect:

Each tablet contains methylparaben sodium 0.68 mg and propylparaben sodium 0.07 mg. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White coloured, capsule-shaped, biconvex, film-coated tablet with a breakline on one side; other side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GABANORT-400 is indicated for the treatment of neuropathic pain in adults.

4.2 Posology and method of administration

Adults

One tablet three times daily (t.d.s.) for oral use. The dose of gabapentin 400 mg t.d.s. corresponds to gabapentin 1200 mg per day, combined with nortriptyline 10 mg t.d.s. (30 mg/day).

Treatment should be initiated at a low dose, titrating upward according to clinical response and tolerability. The lowest effective dose should be used for the shortest duration. Regular reassessment is recommended.

Discontinuation

Gabapentin should not be discontinued abruptly in patients with epilepsy, to avoid precipitating status epilepticus. When stopping treatment in other patients, gabapentin should be gradually tapered (minimum 1 week). Nortriptyline should also be withdrawn gradually.

Renal impairment

Gabapentin is eliminated unchanged by renal excretion. Dose adjustment is required in patients with renal impairment. Nortriptyline: reduce dose and monitor carefully. This fixed-dose combination may not be appropriate for patients with significant renal impairment.

Hepatic impairment

Nortriptyline: careful dosing and, if possible, serum level determination is advisable in patients with hepatic impairment. This combination is contraindicated in severe liver disease.

Elderly patients

Use with caution. Gabapentin clearance is reduced in elderly patients proportionally to creatinine clearance; dose adjustment may be required. The elderly are particularly susceptible to nortriptyline adverse effects, especially agitation, confusion and postural hypotension.

Paediatric population

The safety and efficacy of this combination in patients under 18 years of age have not been established. Nortriptyline is contraindicated in children under 6 years.

Method of administration

Oral. May be taken with or without food.

4.3 Contraindications

- Hypersensitivity to gabapentin, nortriptyline or to any of the excipients listed in section 6.1.

- Recent myocardial infarction.
- Any degree of heart block or other cardiac arrhythmias.
- Severe liver disease.
- Mania.
- Breast-feeding (nortriptyline is contraindicated for the nursing mother).
- Children under 6 years of age (nortriptyline).
- Concomitant use with monoamine oxidase inhibitors (MAOIs); gabapentin/nortriptyline must not be given concurrently with or within 2 weeks of cessation of MAOI therapy.

4.4 Special warnings and precautions for use

Gabapentin — suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents. A meta-analysis of randomised placebo-controlled trials of antiepileptic drugs has shown a small increased risk of suicidal ideation and behaviour. The mechanism is not known and the available data do not exclude the possibility of an increased risk for gabapentin. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment considered. Patients (and caregivers) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge.

Gabapentin — acute pancreatitis

If a patient develops acute pancreatitis under gabapentin treatment, discontinuation should be considered.

Gabapentin — concomitant use with opioids

Cases of respiratory depression and/or sedation have been reported with gabapentin and opioid use. When a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule in healthy volunteers, mean gabapentin AUC increased by 44%. Patients requiring concomitant opioids should be carefully observed for signs of CNS depression and the dose of gabapentin or opioid should be reduced appropriately.

Gabapentin — abuse and dependence

Cases of abuse and dependence have been reported. Patients should be carefully evaluated for a history of drug abuse and observed for possible signs of gabapentin abuse (drug-seeking behaviour, dose escalation, development of tolerance).

Gabapentin — DRESS

Severe, life-threatening Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) has been reported with gabapentin. Early manifestations of hypersensitivity (fever, lymphadenopathy) may be present even without rash. If signs or symptoms are present, the patient should be evaluated immediately; gabapentin should be discontinued if an alternative aetiology cannot be established.

Gabapentin — dipstick proteinuria

False positive readings may be obtained in semi-quantitative determination of total urine protein by dipstick tests. Verification by alternative analytical methods (Biuret method, turbidimetric or dye-binding methods) is recommended.

Nortriptyline — suicide/suicidal thoughts

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. Close supervision should accompany drug therapy, especially in early treatment and following dose changes. A meta-analysis showed an increased risk of suicidal behaviour with antidepressants vs placebo in patients less than 25 years old. Patients and caregivers should monitor for clinical worsening, suicidal behaviour or thoughts and seek medical advice immediately.

Nortriptyline — cardiac effects

Patients with cardiovascular disease should be given nortriptyline only under close supervision, due to its tendency to produce sinus tachycardia and to prolong conduction time. Myocardial infarction, arrhythmia and strokes have occurred. Great care is necessary in hyperthyroid patients or those receiving thyroid medication, as cardiac arrhythmias may develop. QT prolongation risk requires caution when combining with QT-prolonging drugs.

Nortriptyline — epilepsy

The use of nortriptyline should be avoided, if possible, in patients with a history of epilepsy, as nortriptyline is known to lower the convulsive threshold.

Nortriptyline — psychiatric cautions

In schizophrenic patients, nortriptyline may exacerbate psychosis or activate latent schizophrenic symptoms. In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge. Behavioural changes may occur in children receiving treatment for nocturnal enuresis.

Nortriptyline — glaucoma/prostatic hypertrophy

Use of nortriptyline should be avoided, if possible, in patients with narrow-angle glaucoma or symptoms suggestive of prostatic hypertrophy.

Elderly patients

The elderly are particularly susceptible to agitation, confusion and postural hypotension.

Paraben content

This medicinal product contains methylparaben sodium and propylparaben sodium, which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Gabapentin interactions

Opioids (morphine):

Morphine increases gabapentin AUC by approximately 44%; CNS depression risk is increased — careful observation and dose reduction of gabapentin or opioid is required. Concomitant use of opioids is associated with cases of respiratory depression.

Antacids (aluminium/magnesium):

Reduce gabapentin bioavailability by up to 24%. Gabapentin should be taken at least 2 hours after antacid administration.

No pharmacokinetic interaction between gabapentin and phenobarbital, phenytoin, valproic acid, carbamazepine, norethindrone/ethinyl estradiol or probenecid has been observed. A slight decrease in renal excretion with cimetidine is not expected to be of clinical importance.

Nortriptyline interactions

MAOIs (contraindicated):

Hyperpyretic crises, severe convulsions and fatalities have occurred when tricyclic antidepressants were used concurrently with MAOIs. A minimum 2-week interval is required.

Sympathomimetic agents (not recommended):

Nortriptyline should not be given with adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine or phenylpropanolamine.

Antihypertensives (guanethidine, debrisoquine, bethanidine, clonidine — not recommended):

Nortriptyline may decrease the antihypertensive effect. All antihypertensive therapy should be reviewed during TCA treatment.

CYP2D6 inhibitors (fluoxetine, quinidine, antidepressants, phenothiazines, carbamazepine, propafenone, flecainide, encainide):

Nortriptyline metabolism involves the hepatic CYP2D6 isoenzyme; concomitant therapy with drugs metabolised by or inhibiting this enzyme may lead to interactions and require dosage adjustment. Fluoxetine co-administration has produced >2-fold increases in nortriptyline plasma levels; fluoxetine and its active metabolite have half-lives of 4–16 days.

QT-prolonging drugs (barbiturates, alcohol, CNS depressants):

Barbiturates increase the rate of nortriptyline metabolism. Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol; potentiation of excessive alcohol intake may lead to increased suicidal attempts. Cimetidine: may increase steady-state TCA levels.

Anticholinergic drugs:

Supervision and adjustment of dosage required when nortriptyline is used with other anticholinergic agents.

4.6 Fertility, pregnancy and lactation

Gabapentin — Pregnancy

There are no adequate data from the use of gabapentin in pregnant women. Studies in animals have shown reproductive toxicity (embryofoetal developmental effects). Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus. The risk of birth defects is increased by a factor of 2–3 in offspring of mothers treated with antiepileptic medicinal products; this is an important consideration in women of childbearing potential.

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. 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
Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, gabapentin should be used in breast-feeding mothers only if benefits clearly outweigh risks. Nortriptyline is contraindicated in nursing mothers.

Fertility
No adverse effects on fertility or reproduction were observed in rats at gabapentin doses up to 2,000 mg/kg.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor to moderate influence on the ability to drive and use machines; it acts on the CNS and may cause drowsiness, dizziness and other related symptoms, particularly at the beginning of treatment or after dose increases. Nortriptyline may impair mental and/or physical abilities required for performance of hazardous tasks. Patients should be warned accordingly.

4.8 Undesirable effects

Gabapentin — tabulated list of adverse reactions
The following frequencies apply: 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); not known (cannot be estimated from available data — shown in italics).

System Organ Class	Frequency	Adverse Reaction
Infections	Very common / Common	Viral infection (v.c.); pneumonia, respiratory infection, UTI, otitis media, infection (common)
Blood and lymphatic	Common / Not known	Leucopenia (common); thrombocytopenia (not known)
Immune disorders	Uncommon / Not known	Allergic reactions (uncommon); hypersensitivity syndrome, DRESS (not known)
Metabolism	Common / Uncommon / Rare / Not known	Anorexia, increased appetite (common); hyperglycaemia (uncommon); hypoglycaemia (rare); hyponatraemia (not known)
Psychiatric	Common / Not known	Hostility, confusion, emotional lability, depression, anxiety, nervousness (common); hallucinations (not known)
Nervous system	Very common / Common / Uncommon / Rare / Not known	Somnolence, dizziness, ataxia (v.c.); convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, paraesthesia, nystagmus (common); hypokinesia, mental impairment (uncommon); loss of consciousness (rare); other movement disorders — choreoathetosis, dyskinesia, dystonia (not known)
Eye disorders	Common	Visual disturbances (amblyopia, diplopia)
Ear and labyrinth	Common / Not known	Vertigo (common); tinnitus (not known)
Cardiac	Uncommon	Palpitations
Vascular	Common	Hypertension, vasodilatation
Respiratory	Common	Dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Gastrointestinal	Common / Not known	Vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth/throat, flatulence (common); pancreatitis (not known)
Hepatobiliary	Not known	Hepatitis, jaundice
Skin	Common / Not known	Facial oedema, purpura, rash, pruritus, acne (common); SJS, angioedema, erythema multiforme, alopecia, DRESS (not known)
Musculoskeletal	Common / Not known	Arthralgia, myalgia, back pain, twitching (common); rhabdomyolysis, myoclonus (not known)
Renal and urinary	Not known	Acute renal failure, incontinence
Reproductive	Common / Not known	Impotence (common); breast hypertrophy, gynaecomastia, sexual dysfunction (not known)

System Organ Class	Frequency	Adverse Reaction
General	Very common / Common / Uncommon / Not known	Fatigue, fever (v.c.); peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome (common); generalised oedema (uncommon); withdrawal reactions, chest pain, sudden unexplained death (not known)
Investigations	Common / Uncommon / Not known	Decreased WBC, weight gain (common); elevated liver function tests (uncommon); blood CK increased (not known)
Injury and poisoning	Common / Uncommon	Accidental injury, fracture, abrasion (common); fall (uncommon)

Nortriptyline — adverse reactions

Cardiovascular: hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. Psychiatric: confusional states (especially in elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis; suicidal ideation and behaviour. Neurological: numbness, tingling, paraesthesia; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; tinnitus. Anticholinergic: dry mouth, blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus, urinary retention. Allergic: rash, petechiae, urticaria, photosensitisation, oedema, drug fever. Haematological: bone marrow depression including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia. Gastrointestinal: nausea, vomiting, anorexia, diarrhoea, peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus. Endocrine: gynaecomastia; breast enlargement; galactorrhoea; changed libido; impotence; testicular swelling; glucose fluctuations. Other: jaundice; altered liver function, hepatitis; weight changes; sweating; alopecia. Class effects: increased risk of bone fractures (epidemiological data in patients ≥50 years).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

Gabapentin

Acute, life-threatening toxicity has not been observed with overdoses up to 49 g. Symptoms include dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea; all patients have recovered fully with supportive care. Gabapentin overdose, particularly in combination with CNS depressants, may result in coma. Gabapentin can be removed by haemodialysis (usually not required, but indicated in severe renal impairment).

Nortriptyline

50 mg of a tricyclic antidepressant can be an overdose in a child. Symptoms: blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, myoclonic jerks, seizures, respiratory depression, hypotension and cardiac arrhythmias. Cardiac conduction may be slowed with QRS widening, QT prolongation, AV block and ventricular tachyarrhythmias. QRS duration >100 ms is predictive of more severe toxicity. Treatment: symptomatic and supportive. Activated charcoal to reduce absorption. Ventricular arrhythmias may respond to alkalinisation (hyperventilation or sodium bicarbonate). Monitor electrolytes. Seizures may respond to diazepam. Monitoring should continue at least until QRS duration normalises.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics and analgesic combinations. ATC code to be assigned.

Gabapentin

Gabapentin readily enters the brain. It binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels; this binding is proposed to reduce release of excitatory neurotransmitters in regions of the CNS. This activity may underlie gabapentin's anti-seizure and analgesic activity. Gabapentin does not possess affinity for GABA A or GABA B receptors, does not alter GABA metabolism, and does not interact with sodium channels.

Nortriptyline
Nortriptyline is a tricyclic antidepressant and the principal active metabolite of amitriptyline. It inhibits the re-uptake of noradrenaline and serotonin at nerve terminals. It also has ion-channel blocking effects and anticholinergic and sedative properties. The pain-reducing effect in neuropathic pain is not solely linked to its antidepressant properties; noradrenaline reuptake inhibition at the spinal level modulates descending pain inhibitory pathways.

5.2 Pharmacokinetic properties

Gabapentin
Absorption: Peak plasma concentrations observed within 2–3 hours of oral administration. Bioavailability decreases with increasing dose (non-linear absorption). Absolute bioavailability of a 300 mg capsule is approximately 60%. Food has no clinically significant effect on pharmacokinetics. Distribution: Not bound to plasma proteins; volume of distribution 57.7 L. CSF concentrations approximately 20% of corresponding steady-state plasma concentrations. Biotransformation: No evidence of gabapentin metabolism in humans; does not induce hepatic mixed-function oxidase enzymes. Elimination: Eliminated unchanged solely by renal excretion. Elimination half-life independent of dose, averaging 5–7 hours. Gabapentin clearance is directly proportional to creatinine clearance in elderly patients and in those with renal impairment; dose adjustment is required in compromised renal function.

Nortriptyline
Nortriptyline is widely distributed throughout the body and extensively bound to plasma and tissue proteins. Metabolism involves hydroxylation (possibly to active metabolites), N-oxidation and conjugation with glucuronic acid. The metabolism involves CYP2D6 (CYP450IID6 isoenzyme system). Plasma concentrations vary very widely between individuals; no simple correlation with therapeutic response has been established. Half-life is prolonged, supporting once-daily or twice-daily dosing regimens.

5.3 Preclinical safety data

Gabapentin
No genotoxic potential demonstrated. A statistically significant increase in pancreatic acinar cell tumours was found only in male rats at 2,000 mg/kg/day (plasma concentrations 10-fold higher than human levels); these are low-grade malignancies, did not metastasise, and their relevance to human carcinogenic risk is unclear. Gabapentin did not increase malformations in mice, rats or rabbits at therapeutic multiples; delayed ossification effects were observed at 1–5-fold the human dose. No adverse effects on fertility.

Nortriptyline
There are no preclinical data of relevance to the prescriber beyond those already reflected in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

No.	Excipient
1	Maize starch
2	Microcrystalline cellulose (MCCP-101)
3	Povidone K-30 (PVP K-30)
4	Methylparaben sodium (excipient with known effect — 0.68 mg per tablet)
5	Propylparaben sodium (excipient with known effect — 0.07 mg per tablet)
6	Aerosil-200 (colloidal silicon dioxide)
7	Vivasol GF (sodium stearyl fumarate)
8	Talcum
9	Crospovidone XL-10
10	Magnesium stearate
11	Mediicoatt-Uni WT335 white universal (film coat)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C. Keep out of the reach and sight of children.

6.5 Nature and contents of container
ALU-ALU blister packs in unit box with leaflet insert. Pack size: 30 tablets (3×10).

6.6 Special precautions for disposal and other handling
No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
SYMBIOTICA BIOCEUTICALS LTD
P.O. Box 64001-00620, Nairobi, Kenya.

Manufacturer: MARINE MEDICARE PVT. LTD.
Village Kulhariwala, P.O. Mandhala, Tehsil Baddi, District Solan – 174103, Himachal Pradesh, India.

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