

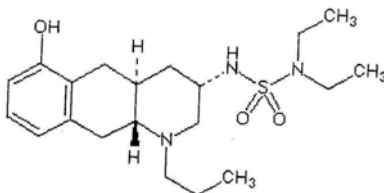
NORPROLAC[®] (quinagolide)

COMPOSITION

Tablets containing 25, 50, 75 or 150 micrograms (0.025, 0.050, 0.075 or 0.150 mg) quinagolide as the hydrochloride.

Norprolac Tablets also contain the following inactive excipients: silica, magnesium stearate, hypromellose, starch-maize, cellulose, lactose, iron oxide red (25 microgram tablet only), indigo carmine (50 microgram tablet only).

DESCRIPTION



Quinagolide hydrochloride is (3 α , 4 α , 10 α)- \pm -N,N-diethyl-N'-(1,2,3,4,4 α ,5,10,10 α -octahydro-6-hydroxy-1-propylbenzo[g]quinolin-3-yl)- sulfamide hydrochloride. It is present in Norprolac as the racemate.

PHARMACOLOGY

Norprolac is a selective dopamine D₂ receptor agonist. Unlike the other dopamine receptor agonists presently available, Norprolac is not an ergot or ergoline compound. Owing to its dopaminergic action, the drug exerts a strong inhibitory effect on the secretion of the anterior pituitary hormone prolactin, but does not reduce normal levels of other pituitary hormones such as luteinising hormone, follicle stimulating hormone, thyrotropin or corticotropin.

As a specific inhibitor of prolactin secretion with a favourable tolerability profile and a prolonged duration of action, Norprolac has been shown to be effective and suitable for once-a-day oral treatment for patients presenting with hyperprolactinaemia and its clinical manifestations. This includes patients who have not responded adequately to other dopamine agonist therapy.

Long-term treatment with Norprolac was found to reduce the size or limit the growth of prolactin-secreting pituitary macroadenomas.

Pharmacokinetics

Absorption:

After oral administration of radiolabelled drug, quinagolide is rapidly and well absorbed. Plasma concentration values obtained by a non-selective radio-immunoassay (RIA), measuring quinagolide together with some of its metabolites, were close to the limit of quantification and gave no reliable information.

Distribution:

The apparent volume of distribution of quinagolide after single oral administration of radiolabelled compound was calculated to be approximately 100 L. The protein binding of quinagolide is approximately 90% and is non-specific.

Metabolism and elimination:

Quinagolide is extensively metabolised during its first pass. For the parent drug, a terminal half-life of 11.5 hours has been calculated under single dose conditions, and of 17 hours at steady state. In blood, quinagolide and its N-desethyl analogue are the biologically active but minor components. Their inactive sulphate or glucuronide conjugates represent the major circulating metabolites. In urine, the main metabolites are the glucuronide and sulphate conjugates of quinagolide and the N-desethyl and N,N-bidesethyl analogues. In the faeces, the unconjugated forms of the three components were found. Studies performed with ³H-labelled quinagolide revealed that more than 95% of the drug is excreted as metabolites. About equal amounts of total radioactivity are found in faeces and urine.

Pharmacodynamics

The most meaningful information on the pharmacokinetic behaviour of quinagolide and its active metabolites can be derived from pharmacodynamic studies in which the reduction in plasma prolactin levels, a reliable marker of drug activity, has been quantified. The results indicate that, with the recommended therapeutic dosage, a clinically significant prolactin-lowering effect occurs within two hours after ingestion, reaches a maximum within four to six hours and is maintained for about 24 hours.

A definite dose-response relationship could be established for the duration, but not for the magnitude, of the prolactin-lowering effect which, with a single oral dose of 50 micrograms, was close to maximum. Higher doses did not result in a considerably greater effect but prolonged its duration.

INDICATIONS

Hyperprolactinaemia (idiopathic or originating from a prolactin-secreting pituitary microadenoma or macroadenoma) associated with its clinical manifestations such as galactorrhoea, oligomenorrhoea, amenorrhoea, infertility and reduced libido.

CONTRAINDICATIONS

- Hypersensitivity to the drug.
- For procedure during pregnancy, see "Use in Pregnancy".
- Impaired hepatic or renal function.

PRECAUTIONS

Fertility may be restored by the treatment with Norprolac. Women of child-bearing age who do not wish to conceive should, therefore, be advised to practice a reliable method of contraception.

*Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease.

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Psychiatric disturbances:

In a few cases, including patients with no previous history of mental illness, treatment with Norprolac has been associated with the occurrence of acute psychosis, usually reversible upon discontinuation. Particular caution is required when Norprolac is given to patients with a history of psychotic disorders.

Hypotension:

Since, especially during the first days of treatment, hypotensive reactions may occasionally occur and result in reduced alertness, patients should be cautious when driving a vehicle or operating machinery. Since orthostatic hypotension may result in syncope, it is recommended that blood pressure be checked both lying and standing during the first days of therapy and following dosage increases.

CNS effects:

Norprolac has been associated with somnolence. Other dopamine agonists have been associated with episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Norprolac. Patients who have experienced somnolence must not drive or operate machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Impaired renal or hepatic function:

To date, no data are available on the use of Norprolac in patients with impaired renal or hepatic function (see "CONTRAINDICATIONS").

Use in Pregnancy (Category B3)

Reproductive studies performed in pregnant rats at oral doses up to 1 mg/kg per day have revealed no evidence of embryotoxicity or teratogenicity to quinagolide. Although, in pregnant rabbits treated with oral doses of up to 3 mg/kg per day, there was a slight increase in the incidence of anomalies in fetuses and litters, the incidence of the individual anomalies do not indicate a teratogenic potential of quinagolide. There were no adequate or well controlled studies in female patients.

In patients wishing to conceive, Norprolac should be discontinued when pregnancy is confirmed, unless there is a medical reason for continuing therapy.

If pregnancy occurs in the presence of a pituitary adenoma and Norprolac treatment has been stopped, close supervision throughout pregnancy is essential. In patients who show symptoms of tumour enlargement (e.g. visual field deterioration or headache), Norprolac treatment may be re-instituted or surgery may be appropriate.

Use in Lactation

Owing to its inhibitory effect on prolactin secretion, Norprolac suppresses lactation. Therefore, mothers receiving the drug cannot breast-feed.

Use in children:

Experience with the use of Norprolac in children is not available.

Carcinogenicity:

A 2-year study in rats showed that dietary administration of quinagolide at doses of 0.01 to 0.2 mg/kg/day increased the incidence of benign Leydig cell tumours in males, and reduced the incidence of mammary gland adenomas and adenocarcinomas and pituitary carcinoma in females and of pituitary adenomas in both sexes. A 90-week study in mice showed that dietary administration at 0.1 and 0.4 mg/kg/day increased the incidences of reproductive tract mesoderm-derived tumours such as leiomyoma and leiomyosarcoma, and stromal polyp and stromal sarcoma. The carcinogenic effects in

*Please note change in Product Information

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rats and mice may involve endocrine mechanisms resulting from disturbances of the hypothalamo-pituitary-gonadal axis secondary to inhibition of prolactin secretion and not predictive of a risk in humans. Gene mutation, cytogenetic and DNA damage assays suggest that quinagolide does not possess mutagenic activity.

Effects on the ability to drive and use machinery:

Patients being treated with Norprolac and presenting with somnolence must be advised not to drive or engage in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until somnolence has resolved (see "PRECAUTIONS-CNS effects").

Since, especially during the first days of treatment, hypotensive reactions may occur and result in decreased alertness, particular care should be exercised when driving a vehicle or operating machinery.

Interactions

No interactions between Norprolac and other drugs have so far been reported. On theoretical grounds, a reduction of the prolactin-lowering effect could be expected when drugs (e.g. neuroleptic agents) with strong dopamine antagonistic properties are used concomitantly.

The tolerability of Norprolac may be reduced by alcohol.

ADVERSE REACTIONS

The adverse reactions reported with the use of Norprolac are characteristic for dopamine receptor agonist therapy. They occur predominantly during the first few days of treatment, are usually not sufficiently serious to require discontinuation of treatment and tend to disappear when treatment is continued.

The most frequent side effects (>10%) are nausea, vomiting, headache, dizziness and fatigue. If necessary, nausea and vomiting may be prevented by the intake of a peripheral dopaminergic antagonist such as domperidone for a few days, at least one hour before the ingestion of Norprolac.

Less frequent side effects (1 to 10%) include anorexia, abdominal pain, constipation or diarrhoea, insomnia, nasal congestion, hypotension and *muscular weakness. Since, on rare occasions, orthostatic hypotension may result in syncope, it is recommended to check blood pressure during the first days of therapy.

In a few isolated cases, treatment with Norprolac has been associated with the occurrence of acute psychosis, reversible upon discontinuation.

In rare cases (<0.1%) Norprolac is associated with somnolence.

*Patients treated with dopamine agonists for treatment of Parkinson's disease, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

DOSAGE AND ADMINISTRATION

Norprolac tablets should be taken once a day at bedtime with some food. The optimal dose must be titrated individually on the basis of the prolactin-lowering effect and tolerability.

With the 'starter pack', treatment begins with 25 micrograms/day for the first three days, followed by 50

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micrograms/day for a further three days. From Day 7 onwards, the recommended dose is 75 micrograms/day. If necessary, the daily dose may then be increased stepwise at intervals not shorter than one week until the optimal individual response is attained.

The usual maintenance dosage is 75 to 150 micrograms/day. Daily doses of 300 micrograms or higher doses are required in less than one-third of the patients. In such cases, the daily dosage may be increased in steps of 75 to 150 micrograms at intervals not shorter than four weeks.

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

OVERDOSAGE

Acute overdosage with Norprolac tablets has not been reported. It would be expected to cause severe nausea, vomiting, headache, dizziness, drowsiness, hypotension and possibly collapse. Hallucinations could also occur.

Treatment would be symptomatic. Metoclopramide could be indicated for the treatment of emesis or hallucinations.

PRESENTATION AND PACKING

Starter pack:

3 tablets 25 micrograms (light pink, "Norprolac" on one side, "25" on the other).

3 tablets 50 micrograms (pale blue, "Norprolac" on one side, "50" on the other).

Maintenance pack:

50 micrograms, packs of 30 (as above) – Not marketed.

75 micrograms, packs of 30 (off-white, "Norprolac" on one side, "75" on the other).

150 micrograms, packs of 30 (off-white, "Norprolac" on one side, "150" on the other) – Not marketed.

Storage: Store below 25°C.

Poison schedule: S4

TGA approved: 27.04.94

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SPONSOR

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