NORPROLAC®

Dopamine-receptor agonist, inhibitor of prolactin secretion

COMPOSITION

Active ingredient: Quinagolide (as the hydrochloride)
Tablets containing 25, 50, 75 or 150 µg

Excipients: Tableting excipients

Colouring agents: E 132 (50 µg tablets only)

PROPERTIES/ACTIONS

Quinagolide, the active ingredient of Norprolac, is a selective dopamine D_2 receptor agonist that does not belong to the chemical class of ergot or ergoline derivatives. As a result of its dopaminergic action quinagolide exerts a potent inhibitory effect on prolactin secretion but does not reduce levels of other pituitary hormones. In certain patients the inhibition of prolactin secretion may be accompanied by a slight and transient increase in plasma somatotropin levels; the clinical significance of this phenomenon is not known.

As a specific inhibitor of prolactin secretion with a prolonged duration of action, Norprolac is an effective once-a-day treatment for hyperprolactinaemia and its clinical manifestations (e.g. galactorrhoea, oligomenorrhoea, amenorrhoea, infertility, reduced libido).

Long-term treatment with Norprolac has been found to reduce the size or restrict the growth of prolactin-secreting pituitary macroadenomas.

PHARMACOKINETICS

Quinagolide was rapidly and readily absorbed following oral administration of tritium-labelled drug. Plasma concentration values obtained by a non-selective radioimmunoassay (RIA) measuring quinagolide and its metabolites were close to the limit of detection and therefore not reliable.

The apparent volume of distribution following a single oral dose of tritium-labelled drug was approx. 100 litres. The terminal half-life of the parent compound was 11.5 hours after a single dose and 17 hours at steady state.

Quinagolide is extensively metabolized during first pass. Studies with tritium-labelled quinagolide have shown that more than 95% of the dose is excreted in the form of metabolites. Approximately equal amounts of total radioactivity were found in the urine and faeces.

The biologically active compounds found in the blood are quinagolide and its analogue N-desethyl; however, these are of minor importance. Their conjugates (glucuronide and sulphate) account for the majority of circulating metabolites. In the urine the main metabolites are the glucuronide and sulphate conjugates of quinagolide and its analogues N-desethyl and N-bidesethyl. The non-conjugated forms of all three compounds are found in the faeces.

Approx. 90% of the drug is bound to proteins; binding is nonspecific.

The results of pharmacodynamic studies show that at the recommended therapeutic dosage a clinically significant prolactin-lowering effect is achieved within 2 hours of ingestion, reaches a peak within 4–6 hours and is maintained for approx. 24 hours.

A definite dose-response relation has been established for the duration, but not the magnitude, of the prolactin-lowering effect. This was virtually maximal following a single oral dose of 50 µg, higher doses producing no increase in degree of effect but only in its duration.

INDICATIONS/USES

Substantiated indications

Hyperprolactinaemia (idiopathic or due to a prolactin-secreting pituitary micro- or macroadenoma).

DOSAGE/ADMINISTRATION

Dopaminergic stimulation may cause symptoms of orthostatic hypotension. Norprolac dosage should therefore be increased gradually using the starter pack and the daily dose taken at bedtime.

Adults

The optimum dose should be titrated individually on the basis of the prolactin-lowering effect and tolerability. With the starter pack treatment begins with 25 µg/day for the first three days, followed by 50 µg/day for a further three days. The recommended dose from day 7 onwards is 75 µg/day. If necessary, the daily dose may be increased stepwise until the optimum individual response is achieved.

The usual maintenance dose is 75 or 150 µg/day. Daily doses of 300 µg or more are required in less than one third of patients. In such cases the daily dosage may be increased in steps of 75–150 µg at intervals of not less than 4 weeks until there is a satisfactory therapeutic response or a reduction in tolerance necessitating withdrawal of therapy.

Patients switching from Parlodel®: Such patients should be switched directly from Parlodel to Norprolac using the starter pack, with subsequent dose increases as described above.

Patients with kidney or liver failure: No data is available for these patients (see Contraindications).

Use in the elderly: There is no experience with the use of Norprolac in elderly patients.

Use in children: There is no experience with the use of Norprolac in children.

RESTRICTIONS ON USE

Contraindications

Hypersensitivity to the drug.

Impairment of liver or kidney function.

For instructions on use during pregnancy see relevant section below.

Precautions

Infertility may be reversed by treatment with Norprolac. Women of childbearing potential who do not wish to become pregnant should therefore be advised to use a reliable method of contraception.

Patients may experience hypotensive reactions leading to reduced alertness, particularly during the first few days of treatment. They should therefore exercise particular caution when driving or using machines.

Since orthostatic hypotension may result in syncope, supine and standing blood pressure should be monitored during the first few days of treatment and following dose increases.

In rare cases, including in patients with no history of mental disturbance, Norprolac therapy has been associated with acute psychosis, normally disappearing on withdrawal of treatment. Particular caution is therefore required when in patients with a history of psychotic disorders.

No data on the use of Norprolac in patients with impaired liver or kidney function is available at present (see **Contraindications**).

PREGNANCY AND LACTATION

Pregnancy

Animal data provide no evidence that Norprolac has any embryotoxic or teratogenic potential but experience with the drug in pregnant women is limited. Women wishing to conceive should stop taking Norprolac as soon as pregnancy is confirmed, unless there is a medical reason for continuing to take it. No increase in the incidence of abortion following withdrawal of treatment at this stage of pregnancy has been observed.

Women with a pituitary adenoma who become pregnant and discontinue Norprolac must be closely monitored throughout the pregnancy.

Lactation

Breastfeeding is normally not possible since Norprolac suppresses lactation. In the event that lactation is not completely suppressed, it is not advisable to breastfeed since it is not known whether quinagolide passes into the breast milk.

ADVERSE REACTIONS

The adverse reactions reported with Norprolac are characteristic of dopamine agonists. They do not normally necessitate withdrawal and tend to disappear spontaneously as treatment is continued.

The most frequently reported adverse reactions (>10%) are nausea, vomiting, headache, dizziness and fatigue. They occur primarily during the first few days of first-time treatment or, transiently, following an increase in dosage. If necessary, nausea and vomiting may be prevented by prescribing a peripheral dopamine antagonist (e.g. domperidone) to be taken at least one hour before ingestion of Norprolac.

The following adverse reactions occur less frequently (1–10%): loss of appetite, abdominal pain, constipation or diarrhoea, insomnia, oedema, flushing, nasal congestion and hypotension. Orthostatic hypotension may result in syncope (see **Precautions**).

Norprolac has been associated with acute psychotic episodes in a few isolated cases, although this effect was reversible on withdrawal of treatment.

INTERACTIONS

To date there have been no reports of interactions between Norprolac and other drugs. In theory, however, concomitant administration of drugs with pronounced dopamine antagonist properties (e.g. neuroleptic agents) could diminish the prolactin-lowering effect of Norprolac. Given that the effect of Norprolac on the 5-HT_1 et 5-HT_2 receptors is 100 times greater than that on D_2 receptors, it is unlikely that there will be any interaction between Norprolac and 5-HT_{1A} receptors. Nevertheless, caution is required in the event of co-administration. There is no evidence of interaction with erythromycin.

The tolerability of Norprolac may be reduced by alcohol.

OVERDOSAGE

No cases of acute overdosage with Norprolac tablets have been reported. The most likely symptoms would be severe nausea vomiting, headache, dizziness, drowsiness, hypotension, and possibly syncope. Hallucinations could also occur. Management should be symptomatic.

OTHER INFORMATION

Norprolac should be stored at a temperature below 25° C.

MANUFACTURER: see folding box.

Information correct at

Approved: 21 August 1998

FERRING
PHARMACEUTICALS