AUSTRALIAN PI - NORPROLAC® (quinagolide) tablets

1 NAME OF THE MEDICINE

quinagolide (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

3 PHARMACEUTICAL FORM

Oral tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the drug.
- For procedure during pregnancy see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION.**
- Impaired hepatic or renal function.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 malabsoption should not take this medicine.

Impulse Control Disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including NORPROLAC. Dose reduction/ tapered discontinuation should be considered if such symptoms develop.

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

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.

Fibrotic complications
NORPROLAC is a non-ergot derived dopaminergic agent. Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived

dopaminergic agents in high doses for Parkinson's disease. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. No increased risk has been reported with use of ergot-derived dopamine agonists in hyperprolactinaemia patients, where a much lower dose is used. These fibrotic complications are believed to be related to the ergoline structure of these compounds. Association with non-ergot derived dopamine agonists is not established. No case of any fibrotic complication associated with NORPROLAC has been reported.

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 **Section 4.3 CONTRAINDICATIONS**).

Use in the elderly
See **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

As the potency of quinagolide for 5-HT_1 and 5-HT_2 receptors is around 100 times lower than that for D_2 receptors, an interaction between NORPROLAC and 5-HT_{1a} receptors is unlikely. However, care should be taken with concomitant use of medication interfering with these receptors.

Due to limited data available with respect to the enzyme(s) involved in the metabolism of quinagolide, potential pharmacokinetic interactions are difficult to predict. Data are also lacking regarding the potential for quinagolide to affect the pharmacokinetics of other medicinal products, e.g. via enzyme inhibition. Caution is therefore recommended if NORPROLAC is used with other medicinal products, in particular with drugs known to be substrates, inducers or inhibitors of drug-metabolising enzymes.

The tolerability of NORPROLAC may be reduced by alcohol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 foetuses 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Impulse control disorders:
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including NORPROLAC. (See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - 'Impulse Control Disorders').

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.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems

4.9 OVERDOSE

Acute overdose 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.

For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Mechanism of action
NORPROLAC is a selective dopamine D_2 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.

Clinical Trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

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 excretion:
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 ^{3}H-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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No genotoxicity studies have been conducted.

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION**.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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).
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).

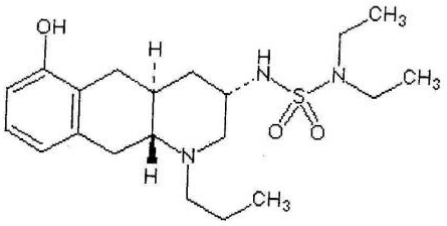
Not all strengths/pack sizes are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



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

CAS Number
94424-50-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll Free: 1800 337 746

9 DATE OF FIRST APPROVAL

26 October 1994

10 DATE OF REVISION

16 October 2019

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

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Summary table of changes

Section Changed	Summary of new information
ALL	Updated PI format to comply with TGA's *Form for providing Product Information*, March 2018 version.