PRODUCT MONOGRAPH

NORPROLAC®

quinagolide hydrochloride

Tablets 0.025 mg, 0.050 mg, 0.075 mg and 0.150 mg

ATC : G02CB04

Prolactin Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 0.025 mg, 0.050 mg, 0.075 mg and 0.150 mg	Silica (colloidal anhydrous), magnesium stearate, methylhydroxy-propylcellulose, maize starch, cellulose (microcrystalline), lactose.

INDICATIONS AND CLINICAL USE

NORPROLAC® is indicated for the treatment of hyperprolactinemia (idiopathic or originating from a prolactin-secreting pituitary microadenoma or macroadenoma)

CONTRAINDICATIONS

Hypersensitivity to the drug and impaired hepatic or renal function. For procedure during pregnancy, see "Use in Pregnancy and Lactation", under PRECAUTIONS.

WARNINGS AND PRECAUTIONS

Warnings

Fertility may be restored in patients receiving treatment with NORPROLAC® (quinagolide hydrochloride). Women of child-bearing age who do not wish to conceive should therefore be advised to practice a reliable method of contraception.

Treatment with NORPROLAC® may effectively lower prolactin levels in patients with pituitary tumours but does not obviate the necessity for radiotherapy or surgical intervention where appropriate.

Caution should be exercised when administering NORPROLAC® to patients with a history of psychotic disorders due to its stimulant effect on D_2 receptors. In a few isolated cases, treatment with NORPROLAC® has been associated with the occurrence of acute psychosis, reversible upon discontinuation.

NORPROLAC® has been associated with somnolence, and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised not to drive or operate machines if they experience any episodes of sudden sleep onset. Furthermore, if sudden onset of sleep does develop, a reduction of dosage or termination or therapy may be necessary.

Effects on ability to drive and use machines

Patients being treated with NORPROLAC® and presenting with somnolence and/or sudden sleep episodes, 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 such recurrent episodes and somnolence have resolved.

Impulse control disorders:

Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers 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.

Precautions

General

Hypotensive reactions may occur during the first few days of treatment with NORPROLAC® (quinagolide hydrochloride) and patients should be cautious when driving a vehicle or operating machinery. Since, on rare occasions, orthostatic hypotension may result in syncope, it is recommended to check blood pressure during the first few days of therapy.

Use in Pregnancy and Lactation:

Animal data provide no evidence that NORPROLAC® has any embryotoxic or teratogenic potential, but experience in pregnant women is still limited. In patients wishing to conceive, NORPROLAC® should be discontinued when pregnancy is confirmed, unless there is a medical reason for continuing therapy. So far, no increased incidence of abortion has been observed following withdrawal of the drug during pregnancy.

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.

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

Carcinogenesis and Mutagenesis

A 2-year carcinogenicity study was conducted in rats using dietary levels of quinagolide hydrochloride equivalent to oral doses of 0.01, 0.06 and 0.2 mg/kg/day. A 90-week study in mice was conducted using dietary levels equivalent to oral doses of 0.02, 0.1 and 0.4 mg/kg/day. The highest doses tested in rats and mice were approximately 10 and 20 times the maximum human oral dose administered in controlled clinical trials (0.9 mg/day equivalent to 0.02 mg/kg/day).

A low incidence of Leydig-cell adenomas in male rats and mesenchymal uterine tumours in mice was observed. The occurrence of these neoplasms is probably attributable to the high luteinizing hormone secretion and estrogen/progesterone ratio that would occur in rodents as a result of the prolactin-inhibiting action of quinagolide. In addition, quinagolide showed no mutagenic or genotoxic potential in various assay systems investigated. The findings in rats and mice were not shown to be relevant for humans due to the fundamental difference in the regulation of the endocrine system between rodents and humans. However, even though there is no known correlation between testicular tumours and uterine malignancies occurring in quinagolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Quinagolide was not embryotoxic or teratogenic in rats and rabbits. Hypoprolactinemia was associated with reduced pregnancy rate and inhibition of lactation of rat dams and slightly retarded but otherwise normal development of rat pups.

Pediatric Use

Safety and effectiveness in children has not been established.

Laboratory Tests

No specific laboratory tests are deemed essential for the management of patients on NORPROLAC® (quinagolide hydrochloride). Periodic routine evaluation of all patients, however, is appropriate.

ADVERSE REACTIONS

The adverse reactions reported with the use of NORPROLAC® (quinagolide hydrochloride) are characteristic for dopamine receptor agonist therapy. The most commonly observed adverse events (>10%) reported during clinical trials with NORPROLAC® were: nausea, vomiting, headache, dizziness and fatigue. Most of these adverse events occur predominantly during the first few days of the initial treatment or, as a mostly transient event, following dosage increase and are usually not sufficiently serious to require discontinuation of treatment and tend to disappear with continued treatment.

Nausea and Vomiting: Nausea and vomiting may be prevented by the intake of a peripheral dopaminergic antagonist, such as domperidone, for a few days, at least 1 hour before the ingestion of NORPROLAC®.

Less frequent side effects (1 to 10%) include anorexia, abdominal pain, constipation or diarrhoea, insomnia, oedema, flushing, nasal congestion and hypotension. Orthostatic hypotension may result in faintness or syncope (see PRECAUTIONS).

In rare cases NORPROLAC® has been associated with somnolence.

Relative to the occurrence of the above-mentioned reactions the following adverse reactions have been less frequently observed in clinical trials involving 549 patients during the first month of treatment. Incidence between 0.5 and 3.5%:

Musculoskeletal:	painful extremities (0.6%)
Respiratory:	nasal congestion (2.4%)
Cardiovascular:	hypotension (1.3%), syncope (0.9%), palpitation (0.7%), flushing (0.6%)
Gastrointestinal:	constipation (3.4%), abdominal pain (3.3%), dyspepsia (1.5%), abdominal discomfort (3.3%), diarrhoea (0.9%)
Central Nervous System:	asthenia (2.9%), anorexia (2.4%), insomnia (2.0%), eye disorders (1.5%), malaise (1.1%), reduced concentration (0.6%)
Miscellaneous:	oedema (1.5%), breast pain (0.9%), mood lability (0.9%), sedation (3.3%), weight gain (0.6%)

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 Warnings and Precautions)

Laboratory Abnormalities: Laboratory parameters may be affected during treatment with NORPROLAC®, but the changes are usually not considered serious. Among the laboratory changes that were reported during clinical trials were increases in bilirubin, serum transaminases, CPK (creatine phosphokinase), potassium, triglycerides and decreases in hematocrit and hemoglobin. These changes were usually transient and rarely of clinical significance.

Only five patients (0.5 %) had to be discontinued from therapy because of laboratory adverse experiences, including one case of neutropenia.

Other: In a few isolated cases, treatment with NORPROLAC® has been associated with acute psychosis, reversible upon discontinuation.

Approximately 200 patients have been treated with NORPROLAC® for longer than four years. There is no evidence that any type of adverse event occurs more frequently with prolonged treatment.

DRUG 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 antagonist properties are used concomitantly.

NORPROLAC® administered concomitantly with antihypertensive agents may have an additive effect on lowering blood pressure. In patients with angina or arrhythmias using antihypertensives, this additional hypotensive effect should be taken into consideration. The tolerability of NORPROLAC® may be reduced by alcohol.

DOSAGE AND ADMINISTRATION

NORPROLAC® (quinagolide hydrochloride) tablets should be taken once a day at bedtime with a snack. The optimal dose must be titrated individually on the basis of the prolactin-lowering effect and patient tolerability.

Recommended Dose and Dosage Adjustment

With the 'starter pack', treatment begins with 0.025 mg/day for the first 3 days, followed by 0.050 mg/day for a further 3 days. From day 7 onwards, the recommended dose is 0.075 mg/day. If necessary, the daily dose may then be increased stepwise at intervals not shorter than 1 week until the optimal individual response is attained. The usual maintenance dosage is 0.075 to 0.150 mg/day. Daily doses of 0.300 mg or higher doses are required in less than one-third of patients. In such cases, the daily dosage may be increased by increments of 0.075 to 0.150 mg at intervals not shorter than 4 weeks. The maximum dose evaluated in efficacy studies was 0.900 mg.

Dosing Considerations

Most adverse events occur predominantly during the first few days of treatment, are usually not sufficiently serious to require discontinuation of treatment and tend to disappear with continued treatment.

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

OVERDOSAGE

No data are available in regard to over dosage in humans with NORPROLAC (quinagolide hydrochloride). However, based on the pharmacological properties of quinagolide, gastrointestinal (nausea, vomiting), CNS (headache, dizziness, drowsiness, hallucinations) and cardiovascular effects (hypotension) might possibly occur. In the event of overdosage, treatment should be symptomatic and supportive.

ACTION AND CLINICAL PHARMACOLOGY

NORPROLAC® (quinagolide hydrochloride) is a selective dopamine D_2 receptor agonist not belonging to the chemical classes of ergot or ergoline compounds.

NORPROLAC® exerts a strong and specific inhibitory effect on prolactin release by acting directly on the prolactin-secreting cells of the anterior pituitary without reducing the levels of other pituitary hormones. In some patients the reduction of prolactin secretion may be accompanied by short-lasting, small increases in plasma growth hormone levels, the clinical significance of which is unknown.

As a specific inhibitor of prolactin secretion with a prolonged duration of action (greater than 24 hours), NORPROLAC® has been shown to be effective for once-a-day oral treatment of patients presenting with hyperprolactinemia and its clinical manifestations. This includes patients in whom treatment with other dopamine agonists was found ineffective or has been associated with unacceptable adverse effects.

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

Quinagolide is rapidly absorbed following oral administration of radiolabelled drug. Quinagolide has an apparent volume of distribution of 100 L. The terminal half-life for parent drug was 11.5 hours following single dose and 17 hours at steady state.

Quinagolide undergoes extensive first pass metabolism. Studies performed with ^{3}H-labelled quinagolide revealed that more than 95% of the drug is excreted as metabolites. Almost equal amounts of total radioactivity were found in faeces (40%) and urine (50%).

In blood, quinagolide and its N-desethyl analogue are the biologically active but minor components. Their sulfate or glucuronide conjugates represent the major circulating metabolites. In urine, the main metabolites are the glucuronide and sulfate conjugates of quinagolide and the N-desethyl, N,N,-didesethyl analogues. In faeces the unconjugated forms of the three compounds were found. The major metabolites in the blood are the N-desethyl and N, N-bidesethyl analogues.

Quinagolide is approximately 90% bound to plasma proteins.

Pharmacodynamic studies using plasma prolactin levels as a reliable marker of drug activity showed that the prolactin-lowering effect of quinagolide at recommended therapeutic doses occurs within 2 hours after ingestion reaches a maximum within 4 to 6 hours and is maintained for at least 24 hours.

In healthy volunteers, the duration of the prolactin-lowering effect is proportional to the dose of quinagolide.

Pharmacokinetics

Quinagolide is rapidly and almost completely absorbed in animals. Almost dose-proportional blood or plasma levels of parent compound and metabolites were observed after single and multiple oral dosing, indicating linear pharmacokinetics. The pharmacokinetics are species-dependent with a terminal half-life varying between 8 hours (rabbit) and 59 hours (dog).

In rats and mice, quinagolide and/or its metabolites were extensively distributed in the extravascular compartment. Target organs were liver, kidneys, salivary glands and pituitary. In pregnant animals the fetal exposure was low due to a limited placental transfer. Elimination of radioactivity from the tissues was rapid and no retention of drug derived material was observed. Quinagolide-derived material was rapidly excreted in all species after single and multiple oral doses. Recovery of drug-derived material is almost complete within 4 days post single dose.

In healthy volunteers, single oral doses of radiolabelled quinagolide (0.025 and 0.05 mg) were rapidly ($t_{1/2}$ absorption $\approx$ 0.1 h) and almost completely absorbed (> 95 % of dose). The absolute bioavailability was low (4 %) due to presystemic metabolism. Peak levels of radioactivity and parent drug were achieved at 0.5-1 hour post-dose. The elimination was biphasic with a terminal half-life of 12 h for parent drug and 24 h for radioactivity. Elimination occurred almost equally via the urine (50 %) and bile (40%). The pharmacokinetics of quinagolide were not altered after repeated administration of 0.075 mg/day for 5 days and an accumulation factor of less than 2 was calculated for parent drug and radioactivity.

STORAGE AND STABILITY

Store between 15^{o} to 30^{o}C. Protect from light and humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets of 0.025 and 0.050 mg are provided in a package intended for initiating therapy (`Starter Pack'). This package is a blister pack containing a total of 6 tablets: 3 X 0.025 mg tablets, 3 X 0.050 mg tablets.

Tablets of 0.075 or 0.150 mg are provided in package intended for maintenance therapy. Tablets of 0.075 mg and 0.150 mg are each supplied in blister packs of 30.

0.025 mg : Each light pink with pigment spots, circular, flat, bevelled edge tablet engraved "25" on one side and "NORPROLAC®" on the other, contains 0.025 mg quinagolide (as the hydrochloride salt).

0.050 mg : Each pale blue with pigment spots, circular, flat bevelled edge tablet engraved "50" on one side and "NORPROLAC®" on the other, contains 0.050 mg quinagolide (as the hydrochloride salt).

0.075 mg : Each whitish, circular, flat bevelled edge tablet engraved "75" on one side and "NORPROLAC®" on the other, contains 0.075 mg quinagolide (as the hydrochloride salt).

0.150 mg : Each whitish, circular, flat bevelled edge tablet engraved "150" on one side and "NORPROLAC®" on the other, contains 0.150 mg quinagolide (as the hydrochloride salt).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

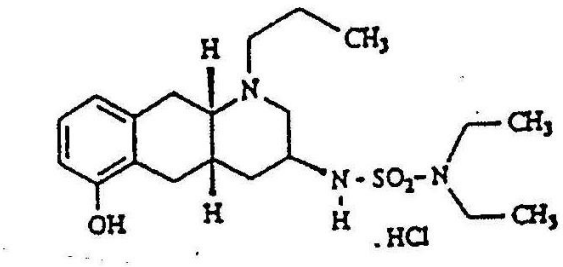
Drug Substance

Proper name: quinagolide hydrochloride

Chemical name: (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

Empirical formula: $C_{20}H_{33}N_3O_3S \bullet HCl$

Structural formula:



Molecular Weight: 432 (salt)

Description: The drug substance is a white to almost-white, finely crystalline powder, which is hygroscopic and light sensitive.

Solubility: Sparingly soluble in water (0.2%) and ethanol (0.1%).

Melting point: With degradation, 231-237°C.

pH of a 1% solution in water/ethanol (1:1 (v/v)): 3.3-5.0

pKa at 20± 2°C in water: 7.65 ± 0.15

CLINICAL TRIALS

Six dose-titration and long-term therapeutic studies were conducted with orally administered quinagolide in a total of 678 patients with hyperprolactinemia of idiopathic or adenomatous origin and its clinical manifestations. Four of the studies were well-controlled double-blind, and randomized trials in hyperprolactinemic women. The other two studies were open label studies involving patients with mostly macroadenemas.

The effect of quinagolide in women with hyperprolactinemia of idiopathic or microadenoma origin was compared to placebo in two of the studies, and to bromocriptine in another two.

The primary endpoint used to evaluate the efficacy of quinagolide treatment was the plasma/serum prolactin concentration at baseline and at various intervals throughout the trials. The dopamine agonist induced decrease of plasma prolactin concentration is usually paralleled by an improvement of the clinical manifestations (Thorner, 1980). The improvement or absence of clinical manifestations of hyperprolactinemia such as amenorrhea, galactorrhea, decreased libido or impotence were used as secondary endpoints. A total of approximately 80% of patients enrolled in the clinical trials were pretreated with dopamine agonists. In these patients, a one-month washout period prior to study entry was necessary to increase plasma prolactin levels at baseline. Success of treatment was based on:

(i) normalization of serum/plasma prolactin ($\leq$ 20 ng/mL)
(ii) regulation of menstrual function
(iii) absence of galactorrhea

Quinagolide was administered at bedtime with a snack in all clinical trials. A starting dose of 0.05 mg quinagolide was used in two of the studies during the double-blind phase. Dosage escalation by monthly increments of 0.025 mg during the open-label phase was based on normalization of prolactin levels and good tolerability.

Hyperprolactinemia of Idiopathic or Microadenoma origins

Results from placebo-controlled double-blind parallel group studies showed that quinagolide at single oral doses of >0.05 mg daily is statistically more effective than placebo ($p<0.001$) in suppressing prolactin plasma levels in hyperprolactinemic women (idiopathic or microadenoma origin) after only 2 weeks of treatment. Normalization of prolactin levels occurred in approximately 70% of patients at doses between 0.05 and 0.075 mg/day.

In the two multicenter double-blind parallel group studies comparing quinagolide to bromocriptine, no clinically or statistically significant difference in efficacy parameters were found between the 2 drugs in suppressing prolactin levels, relieving galactorrhea and restoring gonadal function.

Hyperprolactinemia associated with Macroadenomas

Two open-label multicenter studies were conducted in a total of 228 patients (91 men and 137 women), most of whom had a history or presence of macroadenoma. Baseline serum prolactin levels were widely distributed among patients ranging from 27 to 39,000 ng/mL. In one study, the mean baseline prolactin was 1405 ng/mL.

These studies showed that quinagolide was effective in treating at least 60% of patients with macroadenomas (including those who were previously untreated). Optimal prolactin response was achieved with 12 weeks in approximately 40% of patients while others required up to 12 months to achieve normal prolactin levels. Dose titration steps of 0.075 mg or 0.150 mg quinagolide were well tolerated.

Gross symptomatology such as tumour-related headache, subnormal libido and diminished well-being improved more rapidly than did gonadal function in both men and women.

Clinical symptoms of hyperprolactinemia were relieved or disappeared following quinagolide treatment in males and females. In one study, mild to moderate galactorrhea recorded in 7/65 men (11%) at entry was present in only 2 male patients (4%) up to Month 6 and none at Month 12. At baseline, 23 of the 73 women (32%) had mild to moderate galactorrhea. Galactorrhea was reported in 4/44 (9%) of women at Month 6 and 2/32 (6%) women at Month 12. In the second study, resolution of galactorrhea at month 6 was obtained in 54% of women and all men presenting with this symptom at baseline.

Amenorrhea reported in 90% (56/63) of women at study entry was reported in 36%, 44% and 44% of patients following 3, 9 and 12 months of quinagolide treatment, respectively. Subnormal libido reported in 39% of women at baseline dropped to 25% and 21% at Month 3 and 12 of treatment, respectively. Similarly, 36% (21/59) patients resumed normal menstrual function during the first 6 months of quinagolide treatment in the second study.

Non-migrainous headache judged to be tumour-related was present in 58/138 (42%) of patients at baseline. As the study progressed, this complaint diminished, so that by Month 3 and 6, 17/125 (15%) and 12% of patients reported headache, respectively. 58% (32/55) of macroadenoma patients in the second study had a reduction in the size of their prolactin-secreting pituitary tumour during the course of the study and 78% (7/9) had an improvement in tumour-related visual field deficits after 6 months of quinagolide treatment.

DETAILED PHARMACOLOGY

In vitro

In an in vitro model, designed to test the effect of quinagolide on prolactin secretion by dissociated rat anterior pituitary cells, the drug was shown to have a potent prolactin inhibitory action at picomolar concentrations. The effect mimicked the action of dopamine, the comparative substance.

Selectivity of quinagolide for D_2 receptors was demonstrated both by receptor binding studies and by the use of selective and unselective dopamine antagonists in reversing the quinagolide-induced inhibition of prolactin secretion in vitro.

In vivo

In preclinical studies quinagolide was found to be a potent suppressor of basal and stimulated serum prolactin levels in male and female rats after parenteral and oral administration. Given subcutaneously to rats, quinagolide was found to be approximately 35 times more potent than bromocriptine in preventing ovum implantation (ED_{50}=0.02 mg/kg), a function which in the rat is dependent on prolactin secretion. Given orally to rats, the drug was shown to be approximately 300 times more potent than bromocriptine in suppression of lactation (ED_{50}=0.03 mg/kg). The ID_{50} for inhibition of basal prolactin secretion in male rats was 100 times lower than bromocriptine. Quinagolide inhibited ovulation in rats at a dose 18 times higher than the dose necessary for inhibition of implantation.

Quinagolide also suppressed the reflex release of oxytocin in rats induced by suckling pups. The subcutaneous dose necessary to inhibit milk ejection was 6 times greater than the oral dose for suppression of lactation, so it is unlikely that the inhibition of lactation or nidation is related to the effect on oxytocin.

The cardiovascular actions of quinagolide were examined in anaesthetized cat and dog models. In both models the drug caused blood pressure decreases, with and without reflex tachycardia, at i.v. doses of 4 and 2.5 μg/kg, respectively. In non-anaesthetized hypertensive dogs quinagolide at doses ranging from 5 to 20 μg/kg i.v. prevented the reflex compensatory blood pressure adjustment to sudden postural change.

The drug produced behavioural and biochemical central effects indicating its selective dopamine D_2 receptor stimulating properties. Behavioural effects such as sudden sleep onset episodes and reduced motor activity were observed in rats at doses starting at 0.0003 mg/kg s.c. Quinagolide produced an array of actions within the central nervous system (CNS), i.e., contralateral turning

in rats (> 0.3 mg/kg s.c.) with unilateral lesions of the substantia nigra and inhibition of tetrabenazine induced akinesia (0.3 mg/kg s.c.).

Quinagolide is a racemic compound. Comparative studies of the (+) and (-) enantiomers of quinagolide were conducted in various animal models. The results indicate that its relevant biological activity resides exclusively in the (-) enantiomer. Two putative metabolites of quinagolide were shown to possess pharmacological activity qualitatively similar to quinagolide. The formation of dopaminomimetic metabolites of quinagolide may contribute to the prolonged duration of action seen in man.

TOXICOLOGY

Acute Toxicity Studies

Acute studies were conducted using mice, rats and rabbits by the oral, intraperitoneal and intravenous routes. The following approximate LD_{50} values (mg/kg body weight) were determined:

LD_{50} (mg/kg)			
Species	**P.O**	**I.P**	**I.V**
Mice	**357-> 500**	**158**	**17**
Rats	**> 500**	**> 150**	**13**
Rabbits	**> 150**	**> 50**	**ND***

*** ND : not determined**

Single dose studies indicate the quinagolide has a low acute toxicity compared to its therapeutic dose. No species-specific toxicity occurred. There was some evidence of central depression mainly characterized by ataxia, loss of righting reflex and decreased locomotor activity following each route of administration.

LONG-TERM TOXICITY STUDIES

Rats:

Quinagolide mixed in food was well-tolerated when given to rats at dose levels of 0.06, 0.2, and 0.6 mg/kg for 4 and 13 weeks. With the exception of lower feed intake and reduced body weight gain of the high dose Sprague-Dawley rats used in the 13 week study, findings were limited to the Wistar rats used in the 4 week study and comprised the following: reduced cholesterol levels and increased ovarian weights, partly with increased number and size of corpora lutea, in all treated female rats, as well as lower pituitary weights in females at mid and high dose levels. No morphological changes were detected. Uterine hydrometra were slightly more frequent in treated females. The no-toxic-effect level was between 0.2 and 0.6 mg/kg for both studies.

In a 26-week study with quinagolide at doses levels of 0.05, 0.5 and 2.5-6.0 mg/kg administered twice daily by gavage, findings included: a dose-related decrease in cholesterol levels in all treated females and an increase in the number but not the size of corpora lutea, resulting in enlarged ovaries. Hydrometra and trace to mild uterine endometritis occurred at all dose levels. The no-toxic-effect level in males was 12 mg/kg/day.

The major findings in a one and two-year study in rats were related to the pharmacodynamic action of quinagolide in rodents. At oral doses of 0.01 to 0.2 mg/kg, quinagolide caused a dose-dependent decrease in cholesterol levels as well as uterine metritis and hydrometra associated with squamous metaplasia of the endometrial epithelium in some mid and high dose females. A trend for estrogen dominance as shown by a reduced progesterone/estradiol ratio correlated with an increased number of corpora lutea in the ovaries. Changes observed in the female reproductive tract were linked with reduced LH and prolactin levels: A drug related decrease in palpable masses at 0.01 to 0.2 mg/kg was correlated with decreased prolactin levels. Mean serum LH was decreased in females at 0.06 and 0.2 mg/kg.

In male rats, an increase in luteinizing hormone levels was associated with increased numbers of Leydig cell tumours as was shown for other dopaminergic compounds. Hypoprolactinemia reduces receptor binding capacity of luteinizing hormone in Leydig cells. In male rats, reduced

Leydig cell responsiveness is compensated for by chronically elevated luteinizing hormone secretion to maintain normal testosterone levels.

Mice

In a 90-week lifetime carcinogenicity study in mice, quinagolide (0.02-0.4 mg/kg) administered in feed caused a drug-related decrease in body weight in the high dose group. In addition, an increase in the incidence of mesodermal tumours was observed in the reproductive tract of mid and high dose females (leiomyoma and leiomyosarcoma of the vagina, uterus and cervix, uterine endometrial stromal polyps and sarcomas). A 4-week explanatory hormonal study in female mice showed that quinagolide (0.47, 1.53 mg/kg po) has a hyperestrogenic effect in mice.

The findings in mice and rats were not shown to be relevant for humans due to the fundamental difference in the regulation of the endocrine system between rodents and humans.

Dogs

Quinagolide was associated with a decrease in body weight and with emesis when administered three times daily with escalation of the dose to 1.2 mg/kg in a 26 week study. A 12-month oral study in dogs was conducted at dose levels of 0.02, 0.2 and 0.4-0.8 mg/kg/day. Emetic episodes and excessive salivation occurring in the high dose group precluded further dose escalation. With the exception of reduced body weight gain in the mid and high dose groups, no signs of toxicity occurred. Apart from the emesis observed during the first week, the no-toxic-effect level was 0.02 mg/kg.

REPRODUCTION AND TERATOLOGY STUDIES

Quinagolide was administered by oral gavage for 10 weeks to Sprague-Dawley male rats (0, 5, 50 or 500 μg/kg/day) and for 2 weeks to Sprague-Dawley females (0, 2.5, 5 or 10 μg/kg/day) prior to mating and continued until weaning of the F_1 offspring. Two high dose females were in persistent estrus for 10 and 13 days during mating. A lower pregnancy rate was observed in high dose females. Body weights of high dose F_1 pups were significantly lower and a slight developmental delay was noted. Subsequent mating of the F_1 generation revealed no effects on

reproductive performance or on the development of the F_2 offspring. Effects in females and F_1 offspring were related to the inhibition of prolactin secretion by quinagolide. Implantation inhibition by decreased prolactin levels is a rodent-specific finding.

Pregnant Wistar rats received quinagolide by oral gavage at doses of 0, 0.1, 0.3 and 1.0 mg/kg from days 8 to 15 of gestation. The delayed start of treatment on day 8 served to avoid implantation loss occurring as a result of administering a prolactin secretion inhibiting compound. No embryo- or feto-toxic effects were observed at dose levels up to 1.0 mg/kg (the limit for maternal toxicity), and no adverse effects were noted on F_1 generation fertility and reproductive performance or on the viability and development of the F_2 offspring.

In a further embryotoxicity study, pregnant Russian strain rabbits received quinagolide by oral gavage at doses of 0, 0.3, 1.0 and 3.0 mg/kg from days 6 to 18 of gestation. Quinagolide was well tolerated by the dams and without adverse effect on reproductive performance. Pregnant Sprague Dawley rats received oral doses of quinagolide (0, 5, 25 and 50 μg/kg by gavage) from day 15 of gestation through day 21 postpartum. Despite the low dose levels, neonatal mortality during the lactation period amounted to 66% and 100% in the mid and high dose groups, respectively, as a result of the pharmacodynamic action of quinagolide and lack of milk in the dams.

CARCINOGENICITY STUDIES

Refer to results in chronic toxicity studies.

MUTAGENICITY STUDIES

The ability of quinagolide to induce mutations was examined in vitro with the Ames test using Salmonella typhimurium and various strains of E. coli both with and without activation system. Genotoxicity of the drug was examined in vitro with the unscheduled DNA repair synthesis assay, in Chinese hamster V79 cells, and in vivo in the mouse micronucleus test. Quinagolide showed no mutagenic or genotoxic potential in the assay systems investigated.

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PART III: CONSUMER INFORMATION

NORPROLAC® Tablets
(quinagolide hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when NORPROLAC® Tablets was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NORPROLAC® Tablets. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Your doctor may begin your treatment with the NORPROLAC® STARTER PACK. The NORPROLAC® STARTER PACK is specifically designed to allow your body to gradually adjust to the medicine and lessen the chance of unwanted effects.

What the medication is used for:

NORPROLAC® (quinagolide hydrochloride) belongs to the group of medicines known as prolactin inhibitors. NORPROLAC® is used for the treatment of hyperprolactinemia.

Remember:

- This medicine has been prescribed for your current medical problem only. It must not be given to other people or be used for other problems unless you are otherwise directed by your doctor

What it does:

NORPROLAC® is a medicine used to block the release of a hormone called prolactin. Prolactin is released by a part of the brain called the pituitary gland. NORPROLAC® acts to stimulate dopamine D2 receptors. Stimulation of these receptors results in a decreased level of prolactin in the body. NORPROLAC® is used in the treatment of conditions where there is an excessive level of prolactin in the body (hyperprolactinaemia).

Excess prolactin can result if the pituitary secretes more prolactin than it should or due to the presence of pituitary tumours. Excess prolactin can cause a range of problems such as infertility, menstrual irregularities, loss of sexual function and breast-milk production. With regard to pregnancy, normal ovulation is a complex process that requires many things to happen properly and at the correct time with the proper hormone levels. Often subtle hormonal imbalances or ovulation abnormalities result in decreased fertility (i.e. excessive prolactin levels or hyperprolactinemia). Norprolac can lower prolactin levels and thus restore fertility.

It may take several weeks for NORPROLAC® to work.

When it should not be used:

Do not take Norprolac if you have an allergy to:
* quinagolide (the active ingredient) or any of the other ingredients.

Do not take this medicine if you have problems with your kidneys or liver.
There is no experience with the use of this medicine in people whose kidney or liver function is impaired.

What the medicinal ingredient is:

quinagolide hydrochloride

What the nonmedicinal ingredients are:

Silica (colloidal anhydrous), magnesium stearate, methylhydroxy-propylcellulose, maize starch, cellulose (microcrystalline), lactose.

What dosage forms it comes in:

0.025 mg, 0.050 mg, 0.075 mg and 0.150 mg Tablets

WARNINGS AND PRECAUTIONS

NORPROLAC® has been associated with somnolence, and episodes of sudden sleep onset. Do not drive or operate machines if you experience any episodes of sudden sleep onset or drowsiness. Contact your doctor if sudden onset of sleep occurs as a reduction of dosage or termination or therapy may be necessary.

Hypotensive reactions or dizziness may occur during the first few days of treatment with NORPROLAC® (quinagolide hydrochloride) and patients should be cautious when driving a vehicle or operating machinery.

Talk to your doctor if you have any of the following behavioural change:

- abnormal gambling habits,
- increase sexual drive or desire,
- extremely frequent or suddenly increased sexual urges or sexual activity,
- obsession with shopping and buying behaviour
- eating muchmore rapidly than normal until feeling uncomfortably full and/or not feeling physically hungry, a sense of being out of control

Pregnancy: Women of childbearing age who do not wish to conceive should practice a reliable method of contraception.

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

BEFORE you use NORPROLAC® talk to your doctor or pharmacist if:

- if you intend to breast-feed an infant since this medication stops milk from being produced
- if you have any of the following medical problems: liver disease, severe renal disease, mental problems (history of)

INTERACTIONS WITH THIS MEDICATION

Let your doctor or pharmacist know about your alcohol consumption and any medication you take including the medications you have bought without prescription.

If you are now taking any of the following medicines or types of medicines let your doctor or pharmacist know.

- Blood pressure-lowering medication
- Birth control pills
- Drugs intended to treat mood disorders and generally prescribed by psychiatrists
- Drugs intended to treat Parkinson's disease and generally prescribed by neurologists

PROPER USE OF THIS MEDICATION

Unless otherwise directed by your doctor take this medicine at bedtime, you can have a snack or a full glass of milk to reduce stomach irritation. If stomach upset continues, check with your doctor. In order for this medicine to work it should be taken as directed.

It is important that your doctor checks your progress at regular visits to make sure that this medicine is working and check for unwanted effects.

Usual dose:

The amount of NORPROLAC® you will need depends on your body's needs and individual tolerance. Your doctor will advise you on the correct dosage regimen for you. The usual starting dosage prescribed is 0.025 mg (pink tablets) once-a-day for the first three days, followed by the higher dosage 0.050 mg (blue tablets) once-a-day for a further three days. From Day 7 onwards the usual maintenance dosage is 0.075 to 0.150 mg/day with a snack at bedtime.

Should you experience any intolerance at any of these dose levels, discuss it with your doctor before proceeding to the following dose level. During treatment your doctor may decide to adjust the dosage according to the response to the medication.

Overdose:

There is no information on overdosage in humans with NORPROLAC (quinagolide hydrochloride). However based on the knowledge of this type of drug, symptoms such as nausea, vomiting, headache, dizziness, drowsiness, hallucinations and hypotension might possibly occur. In the event of overdosage go to your emergency room and bring the medication bottle with you or contact you local Poison Control Centre.

Missed dose:

If you miss a dose of this medicine take it as soon as possible. If it is almost time for your next dose, do not take the missed dose and do not double the next one. Instead go back to your regular dosing schedule. If you miss more than 2 or 3 doses in a row or if you have any questions about this, check with your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The adverse reactions reported with the use of NORPROLAC® (quinagolide hydrochloride) are characteristic of this group of medicines. The most commonly observed adverse events (more than10%) reported during clinical trials with NORPROLAC® were: nausea, vomiting, headache, dizziness and fatigue. Most of these adverse events occur predominantly during the first few days of the initial treatment or, as a mostly transient event.

You may also experience anorexia, abdominal pain, constipation or diarrhoea, insomnia, oedema, palpitations, flushing, nasal congestion, hypotension on standing and hypotension.

In rare cases NORPROLAC® has been associated with sudden onset of sleep or drowsiness.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
Less Common (less than 2%)*	**Drowsiness or sudden onset of sleep / somnolence**		√	
	Faintness		√	
	Acute Psychosis		√	
	Eye disorders		√	
	Breast Pain		√	
	Allergic Reaction (Hypersensitivity)			√

*** Percentages reported represent the expected occurrence in 100 people**

This is not a complete list of side effects. For any unexpected effects while taking* NORPROLAC®, *contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15° to 30°C. Protect from light and humidity. Keep all medicines out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Ferring Inc., at:
1-800-263-4057

This leaflet was prepared by Ferring Inc.

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