SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NORPROLAC® 75 micrograms Tablets
Quinagolide 75 micrograms Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinagolide, as the hydrochloride, 75 micrograms

3 PHARMACEUTICAL FORM

Tablet for oral administration

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hyperprolactinaemia (idiopathic or originating from a prolactin-secreting pituitary microadenoma or macroadenoma).

4.2 Posology and method of administration

Since dopaminergic stimulation may lead to symptoms of orthostatic hypotension, the dosage of NORPROLAC should be initiated gradually with the aid of the 'starter pack', and given only at bedtime.

Adults
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 3 days, followed by 50 micrograms/day for a further 3 days. From day 7 onwards, the recommended dose is 75 micrograms/day.

If necessary, the daily dose may then be increased stepwise 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 4 weeks until satisfactory therapeutic effectiveness is achieved or reduced tolerability, requiring the discontinuation of treatment, occurs.

Elderly
Experience with the use of NORPROLAC in elderly patients is not available.

Children
Experience with the use of NORPROLAC in children is not available.

Method of Administration
NORPROLAC should be taken once a day with some food at bedtime.

4.3 Contraindications

Hypersensitivity to the drug.
Impaired hepatic or renal function
For procedure during pregnancy, (see section 4.6 Pregnancy and lactation).

4.4. Special warnings and precautions for use

Fertility may be restored by 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.

Since orthostatic hypotension may result in syncope, it is recommended to check blood pressure both lying and standing during the first days of therapy and following dosage increases.

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 in patients who have had psychotic episodes in their previous history.

To date no data is available with the use of NORPROLAC in patients with impaired renal or hepatic function (see Section 4.3 Contraindications).

NORPROLAC has been associated with somnolence. Other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst 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 (see Section 4.7 Effects on the ability to drive and use machines).

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.

Dopamine agonist withdrawal syndrome (DAWS) has been reported following discontinuation of dopamine agonists. Non-motor adverse effects may occur when discontinuing dopamine agonists. Symptoms which have been reported with other dopamine agonists include apathy, anxiety, depression, fatigue, sweating and pain which may be severe. When treatment with quinagolide is stopped there is a possible risk that DAWS may occur in some patients. Patients could therefore benefit from tapering of the quinagolide dose.

NORPROLAC should be kept out of the reach and sight of children.

4.5 Interaction with other medicinal products and other forms of interaction

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 NORPROLAC for 5-HT_1 and 5-HT_2 receptors is some 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 when using these medicaments concomitantly.

The tolerability of NORPROLAC may be reduced by alcohol.

4.6 Fertility, Pregnancy and lactation

<u>Pregnancy</u>

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. No increased incidence of abortion has been observed following withdrawal of the drug at this point.

If pregnancy occurs in the presence of a pituitary adenoma and NORPROLAC treatment has been stopped, close supervision throughout pregnancy is essential.

Lactation
Breast-feeding is usually not possible since NORPROLAC suppresses lactation. If lactation should continue during treatment, breast-feeding cannot be recommended because it is not known whether quinagolide passes into human breast milk.

4.7 Effects on ability to drive and use machines

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.

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) unless patients have overcome such experiences of somnolence (see 4.4 Special warnings and precautions for use).

4.8 Undesirable effects

Frequency estimate: very common ≥10%, common ≥1% to <10%, uncommon ≥0.1% to <1%, rare ≥0.01% to <0.1%, very rare <0.01%.

The adverse reactions reported with the use of NORPROLAC are characteristic for dopamine receptor agonist therapy. They are usually not sufficiently serious to require discontinuation of treatment and tend to disappear when treatment is continued.

Very common undesirable effects are nausea, vomiting, headache, dizziness and fatigue. They occur predominantly during the first few days of the initial treatment or, as a mostly transient event, following dosage increase. 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 1 hour before ingestion of NORPROLAC.

Common undesirable effects include anorexia, abdominal pain, constipation or diarrhoea, insomnia, oedema, flushing, nasal congestion and hypotension. Orthostatic hypotension may result in faintness or syncope (see 4.4 Special warnings and precautions for use).

Rarely NORPROLAC has been associated with somnolence.

In very rare cases, treatment with NORPROLAC has been associated with the occurrence of acute psychosis, reversible upon discontinuation.

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').

4.9 Overdose

Symptoms: 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: Should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: prolactin inhibitors (ATC code G02C B04)

Quinagolide, the active ingredient of NORPROLAC, is a selective dopamine D_2-receptor agonist not belonging to the chemical classes of ergot or ergoline compounds. 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. 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, NORPROLAC has been shown to be effective and suitable for once-a-

day oral treatment of patients presenting with hyperprolactinaemia and its clinical manifestations such as galactorrhoea, oligomenorrhoea, amenorrhoea, infertility and reduced libido.

5.2 Pharmacokinetic properties

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.

The apparent volume of distribution of quinagolide after single oral administration of radiolabelled compound was calculated to be approx. 100 L. 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.

Quinagolide is extensively metabolised during its first pass. 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.

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, N,N-didesethyl analogues. In the faeces the unconjugated forms of the three components were found.

The protein binding of quinagolide is approximately 90% and is non-specific.

The results, obtained in pharmacodynamic studies, indicate that with the recommended therapeutic dosage a clinically significant prolactin-lowering effect occurs within 2 hours after ingestion, reaches a maximum within 4 to 6 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.

5.3 Preclinical safety data

<u>Acute toxicity</u>

The LD_{50} of quinagolide was determined for several species after single oral administration: mice 357 to > 500 mg/kg; rats > 500 mg/kg; rabbits > 150 mg/kg.

Chronic toxicity
Decreased cholesterol levels of treated female rats suggest that quinagoilde influences lipid metabolism. Since similar observations have been made with other dopaminergic drugs, a causal relationship with low prolactin levels is assumed. In several chronic studies with rats, enlarged ovaries resulting from an increased number of corpora lutea and, additionally, hydrometra and endometritis were observed. These changes were reversible and reflect the pharmacodynamic effect of quinagolide: suppression of prolactin secretion inhibits luteolysis in rats and thus influences the normal sexual cycle. In humans, however, prolactin is not involved in luteolysis.

Carcinogenic and mutagenic potential
In comprehensive *in vitro* and *in vivo* mutagenic studies there was no evidence of a mutagenic effect.

The changes which were observed in carcinogenicity studies reflect the pharmacodynamic activity of quinagolide. The drug modulates the prolactin level as well as, specially in male rats, the level of luteinizing hormone and, in female rodents, the ratio of progesterone to oestrogen.

Long-term studies with high doses of quinagolide revealed Leydig cell tumours in rats and mesenchymal uterine tumours in mice. The incidence of Leydig cell tumours in a carcinogenicity study in rats was increased even at low doses (0.01 mg/kg). These results were without relevance for the therapeutic application in humans since there are fundamental differences between humans and rodents in the regulation of the endocrine system.

Reproductive toxicity
Animal studies in rats and rabbits showed no evidence for embryotoxic or teratogenic effects. The prolactin inhibiting effect led to a decrease of milk production in rats, which was associated with an increased loss of rat pups. Possible post-natal effects of exposure during fetal development (2nd and 3rd trimester) and effects on female fertility are not sufficiently investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous; magnesium stearate; methylhydroxypropylcellulose; maize starch; cellulose, microcrystalline; lactose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life is 5 years. The expiry date is printed on the box. On the blister the expiry date is marked with the letters EXP.

6.4 Special precautions for storage

The expiry date refers to original unopened boxes, which were stored below 25°C. No special warning with respect to light sensitivity or humidity is necessary because the tablets are protected by the packaging.

6.5 Nature and contents of container

The 75 micrograms tablets are in packs of 30 tablets (3 times 10 tablets) in aluminium blisters.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 35533/0064

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15th December 2004

10 DATE OF REVISION OF THE TEXT

24/12/2019