1. NAME OF THE MEDICINAL PRODUCT

NORPROLAC 25 microgram + 50 microgram tablets
NORPROLAC 75 microgram tablets
NORPROLAC 150 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet 25 microgram contains: 25 microgram of quinagolide as quinagolide hydrochloride.

1 tablet 50 microgram contains: 50 microgram of quinagolide as quinagolide hydrochloride.

1 tablet 75 microgram contains: 75 microgram of quinagolide as quinagolide hydrochloride.

1 tablet 150 microgram contains:150 microgram of quinagolide as quinagolide hydrochloride.

Excipient(s) with known effect:
Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

25 microgram:	Light pink with isolated pigment spots, circular, flat, bevelled edge, 7 mm in diameter. Inscriptions: “NORPROLAC” circular on one side and “25” linear on the other side.
50 microgram:	Light blue with isolated pigment spots, circular, flat, bevelled edge, 7 mm in diameter. Inscriptions: “NORPROLAC” circular on one side and “50” linear on the other side.
75 microgram:	White, circular, flat, bevelled edge, 7 mm in diameter. Inscriptions: “NORPROLAC” circular on one side and “75” linear on the other side.
150 microgram:	White, circular, flat, bevelled edge, 9 mm in diameter. Inscriptions: “NORPROLAC” circular on one side and “150” linear on the other side.

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

Posology

Since dopaminergic stimulation may lead to symptoms of orthostatic hypotension, the dosage of NORPROLAC should be initiated gradually with the aid of the titration pack, and given once daily in the

evening with food. The optimal dose must be titrated individually on the basis of the prolactin-lowering effect and tolerability.

Adults
With the titration 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.

When required, the daily dose may be increased in steps of 75 micrograms at intervals not shorter than one week until the optimal individual response is attained. The usual maintenance dosage is 75 micrograms/day or 150 micrograms/day. Single patients may require daily doses of 300 micrograms or higher. In such cases, the daily dosage may be increased in steps of 75 micrograms to 150 micrograms at intervals not shorter than 4 weeks until satisfactory therapeutic effectiveness is achieved or reduced tolerability limits further increases in the dose.

Eldery population
The experience in elderly is limited (see section 4.4).

Paediatric population
The experience in children is limited (see section 4.4).

4.3 Contraindications

Severely impaired hepatic or renal function. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hyperprolactinaemia may be physiological (pregnancy, lactation) as well as be due to other causes among others tumours in hypothalamus or pituitary gland and a number of drugs. Therefore it is important that the specific cause to a hyperprolactinaemia is explained as far as possible and that causal therapy is initiated.

Since orthostatic hypotension may result in syncope in rare cases, it is recommended to check blood pressure both lying and standing during the first days of therapy and following dosage increases.
Moreover, orthostatic blood pressure changes with reflex increases in heart rate might be relevant for patients with severe heart diseases.

In women suffering from prolactin-related fertility disorders, 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.

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.

NORPROLAC has been associated with somnolence. Other dopamine agonists have been associated with sudden sleep onset episodes, particularly in patients with Parkinson’s disease. Patients must be informed of this and advised to be cautious 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.

No interaction studies have been performed with quinagolide and caution is therefore recommended if NORPROLAC is combined with other medicinal products (see section 4.5).

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

The tolerability of NORPROLAC may be reduced by alcohol.

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.

A limited number of elderly patients have been treated for pituitary adenomas and rheumatoid arthritis with quinagolide at doses ranging from 50 – 300 μg/day. The duration of treatment ranged from 6 – 93 months and the treatment was well-tolerated.

A limited number of children aged 7-17 years have been treated with NORPROLAC for prolactinoma, at doses ranging from 75 – 600 μg/day. The duration of treatment ranged from 1 – 5 years and the treatment was well-tolerated.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed and 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-HT1 and 5-HT2 receptors is some 100 times lower than that for D2 receptors, an interaction between NORPROLAC and 5-HT1 a 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 is 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 combined with other medicinal products, in particular with drugs known to be potent inhibitors of drug-metabolising enzymes.

The tolerability of NORPROLAC may be reduced by alcohol.

4.6 Fertility, pregnancy and lactation

Fertility: In women suffering from prolactin-related fertility disorders, 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 (See section 4.4).

Pregnancy*:* Animal data provide no evidence that NORPROLAC has any embryotoxic or teratogenic potential, but clinical experience in pregnant women is 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

Treatment with NORPROLAC may, in some patients, impair the ability to react during the first days of treatment. This has to be taken into consideration when sharpened alertness is demanded, e.g. when driving. Patients being treated with NORPROLAC and presenting with somnolence and/or sudden sleep onset 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 these episodes or the somnolence have ceased.
See also section 4.4.

4.8 Undesirable effects

Most adverse reactions are dose-dependent and transient. The adverse reactions are seldom sufficiently serious to require discontinuation of treatment.

MedDRA Organ Class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Rare** (≥1/10,000 to <1/1,000)
Metabolism and nutrition disorders	-	Anorexia	-
Psychiatric disorders	-	Insomnia	Reversible acute psychosis
Nervous system disorders	Dizziness, headache	-	Somnolence
Vascular disorders	-	Orthostatic hypotension	-
Respiratory, thoracic and mediastenal disorders	-	Nasal congestion	-
Gastrointestinal disorders	Nausea, vomiting	Abdominal pain, constipation, diarrhoea	-
Musculoskeletal, connective tissue and bone disorders	-	Muscular weakness	-
General disorders and administration site conditions	Fatigue	-	-

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’).

Orthostatic hypotension reported following use of NORPROLAC, rarely can result in syncope.

The risk of hypersensitive reactions could not be excluded.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via *<the national reporting system> <[to be completed nationally]>*

4.9 Overdose

Limited experience of overdose. It would be expected to cause nausea, vomiting, headache, dizziness, drowsiness, hypotension, hallucinations. Treatment of overdose should be symptomatic. If justified stomach wash-out or carbon.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine receptor agonist, prolactin inhibitors
ATC code: G02CB04.

Quinagolide is a selective dopamine D_2-receptor agonist. Quinagolide exerts an inhibitory effect on the secretion of prolactin, but does not reduce normal levels of other pituitary hormones. Reduction of the prolactin level occurs within 2 hours after ingestion, reaches a maximum within 4 to 6 hours and is maintained for about 24 hours. The duration is dose-dependent.
Long-term treatment with NORPROLAC was found to reduce the size or limit the growth of prolactin-secreting pituitary macro- and microadenomas.

5.2 Pharmacokinetic properties

Since intravenous studies have not been possible to perform, information on absolute bioavailability, clearance and volume of distribution is lacking. Quinagolide is rapidly absorbed. The influence of concomitant food intake on absorption has not been studied. Maximal plasma concentration (about 10 picogram/ml at steady-state) was reached after 30 minutes when 75 micrograms quinagolide was given. The protein binding of the substance is approximately 90% and is non-specific. The elimination half-life is about 11 hours (single dose) and 17 hours at steady-state. The metabolism of quinagolide is extensive. Quinagolide and its N-desethyl analogue occur in small amounts in the blood, about one tenth of the total radioactivity. The N-desethyl analogue has pharmacological effect similar to the parent substance but is less potent and does probably not contribute to the clinical effect. The sulphate and 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 faeces the unconjugated forms of the three components were found.
The pharmacokinetics have not been studied in elderly patients or in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

In comprehensive *in vitro* and *in vivo* mutagenic studies performed with quinagolide, there was no evidence of a mutagenic effect. Carcinogenicity studies showed an increase in tumours of the female mouse reproductive tract and of benign Leydig cell adenomas in rats. These findings are the consequences of the central dopaminergic effects of the long-lasting inhibition of prolactin in rodents with a specific hormonal physiology different to man. Consequently these effects are not regarded as relevant to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 tablet 25 microgram contains:
Lactose monohydrate
Microcrystalline cellulose
Maize starch
Hypromellose
Magnesium stearate
Anhydrous colloidal silica
Red iron oxide (E172)

1 tablet 50 microgram contains:
Lactose monohydrate
Microcrystalline cellulose
Maize starch
Hypromellose
Magnesium stearate
Anhydrous colloidal silica
Indigo carmine (E132)

1 tablet 75 microgram contains:
Lactose monohydrate
Microcrystalline cellulose
Maize starch
Hypromellose
Magnesium stearate
Anhydrous colloidal silica

1 tablet 150 microgram contains:
Lactose monohydrate
Microcrystalline cellulose
Maize starch
Hypromellose
Magnesium stearate
Anhydrous colloidal silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Pack sizes:
Titration package 25+50 microgram, 3+3 tablets
Packed in a blister of ALU/PVC/PVDC which is sealed in a moisture-proof aluminium bag.

75 microgram 30 tablets
150 microgram 30 tablets
Packed in blisters of ALU/ALU

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2015-10-14
<[To be completed nationally]>