SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pyridostigmine bromide NRIM 60mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each coated tablet contains 60mg of Pyridostigmine bromide.

Excipients with known effect:
- Lactose (as monohydrate) 49.36 mg
- Sucrose 72.501 mg
- Aspartame (E951) 0.25 mg
- Sunset Yellow FCF (E110) 0.16575 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Coated Tablet

Light orange to orange round, biconvex, coated tablets imprinted in black with PY60 on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Pyridostigmine bromide NRIM is indicated for the treatment of Myasthenia gravis.

4.2 Posology and method of administration

Adults
The usual dose is 60mg-180mg pyridostigmine bromide two to four times daily.

Generally, the dosage and frequency of daily intake, depends on the severity of the disease and patient response to treatment and should be strictly individualized. The dosage recommendations can therefore serve as a guide.

Caution should be exercised when using high-dose regimens (see section 4.4).
Renal impairment
Patients with renal impairment may need lower doses. The required dose should be determined on a case-by-case basis according to clinical effects (see also section 4.4).

Method of administration
The coated tablets are for oral use. The coated tablets should be taken with some liquid (preferably with half a glass to a full glass of water).

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Mechanical obstruction of the intestinal or urinary tract, and all disorders accompanied by an increased bronchial muscle tone, i.e. spastic bronchitis and bronchial asthma;
- During breast-feeding (see also section 4.6).

4.4 Special warnings and precautions for use
The benefit of treatment should be carefully weighed against the increased risk in the following conditions: gastric ulcer, thyrotoxicosis, decompensated heart failure, myocardial infarction.

Pyridostigmine bromide should be used with caution if the patient is on a high-dose succinylcholine regimen, since this may lead to an augmentation of the neuromuscular blockade instead of to its intended reversal (see also section 4.5).

Special caution should be exercised when administering Pyridostigmine bromide to patients with bradycardia and to patients who have undergone gastrointestinal surgery.

Pyridostigmine bromide is eliminated primarily by renal excretion in an unchanged form. Hence, it should be used with caution in patients with renal impairment (see also section 4.2).

Clinical symptoms observed in refractory cases (myasthenic crisis) and those seen in an overdose (cholinergic crisis) are similar. Hence, if high doses have been administered and typical symptoms appear, further work-up with a relevant test should be carried out while observing the essential precautions (see also section 4.2).

This medicinal product contains the following excipients.
Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
Sunset yellow FCF (E110): may cause allergic reaction.
Aspartame (E951): this contains a source of phenylalanine. May be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction
Pyridostigmine bromide may prolong the inhibitory effects of succinylcholine (see section 4.4).

Concomitant administration of Pyridostigmine bromide (coated) and external application of N, N-diethyl-meta-toluamide (DEET) to large skin areas should be avoided

Methylcellulose prevents the absorption of pyridostigmine bromide. Concomitant use of medicinal products which contain methylcellulose as an excipient should therefore be avoided.

4.6 Fertility, pregnancy and lactation
There is no or limited amount of data from the use of pyridostigmine bromide in pregnant women.

Intravenous administration of anticholinesterases during pregnancy may lead to premature uterine contractions. The risk of premature contractions is especially high when the product is administered towards the end of the gestation period. It is unknown whether oral administration is also associated with an increased risk of premature uterine contractions.

Animal studies revealed no teratogenic effects of orally administered pyridostigmine bromide. However, fetotoxicity and effects on the offspring have been observed (see sections 5.3).

Therefore, Pyridostigmine bromide is not recommended during pregnancy unless strongly indicated.

Breast-feeding:
Since pyridostigmine bromide is excreted in human milk, treatment with Pyridostigmine bromide is contraindicated during breast-feeding. If such treatment is absolutely required, breast-feeding should be discontinued (see also section 4.3).

4.7 Effects on ability to drive and use machines
Pyridostigmine bromide has no or negligible influence on the ability to drive or use machines.
Impairment of the ability to drive and/or use machines cannot be ruled out due to the fact that the underlying illness may not be fully compensated or
parasympathomimetic (vagotonic) effects of a relative overdose of Pyridostigmine bromide may take effect.

4.8 Undesirable effects

There are very limited clinical studies conducted on the use of pyridostigmine. In post marketing data the most common undesirable effects were gastrointestinal, being nausea, vomiting, increase salivaion, diarrhoea and abdominal cramping. Listed below are the adverse reactions associated with the use of pyridostigmine.

The following frequency conventions were adopted:

Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Eye disorders

Not known
Disturbance in accommodation, lacrimation

Cardiac disorders

Not known
Bradycardia as well as adverse cardiovascular reactions and hypotension

Respiratory, thoracic and mediastinal disorders

Not known
Increased bronchial secretions

Gastrointestinal disorders

Not known
Diarrhoea, abdominal cramping (increased bowel movements), vomiting, nausea, salivation

Skin and subcutaneous tissue disorders

Very rare
Skin rash

Musculoskeletal and connective tissue disorders

Not known
Muscle weakness (see section 4.9), muscle spasms, muscle fasciculations

Renal and urinary disorders

Not known
Increased urinary urgency

General disorders and administration site conditions

Not known
Diaphoresis
Special patient populations:
Patients with chronic obstructive pulmonary disease (COPD) may display signs of pulmonary obstruction in addition to increased bronchial secretions.

Asthma patients may experience respiratory tract symptoms.

In patients with intracranial abnormalities, therapy with pyridostigmine bromide may trigger psychopathological symptoms, even psychosis; alternatively, pre-existing symptoms may worsen.

The symptoms may be a sign of cholinergic crisis. If parasympathomimetic effects appear, the antidote to be used is parenteral atropine sulfate (see section 4.9).

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 listed in Appendix V.

4.9 Overdose
An overdose of Pyridostigmine Bromide may lead to cholinergic crisis, which manifests among other signs as severe or increased muscle weakness. If such a situation is ignored, it can result in muscular paralysis or respiratory death. Bradycardia, cardiovascular adverse reactions, periodic sinus tachycardia and hypotension may be other side effects.

Countermeasures are immediate discontinuation of Pyridostigmine Bromide and doses of 1 to 2 mg atropine sulphate intravenously slowly. Depending on the pulse rate this dose can be repeated after two to four hours.

An overdose can lead to cholinergic crisis, which requires intensive medical monitoring.

The symptoms are:
Salivation, lacrimation, rhinorrhea, severe sweating, flushing, adynamia, miosis and accommodation disturbances, dizziness, vomiting, involuntary urination and defecation with tenesmus, extreme bradycardia to cardiac arrest, hypotension and circulatory collapse, bronchospasm, pulmonary edema, occasional convulsions.

Treatment of cholinergic crisis:
In the event of cholinergic crisis the following procedure should be followed, the input of an emergency or specialist physician should be sought. The acetylcholinesterase inhibitor should be discontinued for 3 to 4 days. Atropine should be given and the dose should be reduced according to clinical features. Plasma therapy should not be given. Depending on the severity or degree of the overdose, consideration to bronchiolar lavage, IV fluids, mucolytics and broncholytics should be given. Once the patient shows signs of a stable
recovery careful reformulation of the acetylcholinesterase inhibitor therapy, for example, starting with 0.5 mg of pyridostigmine bromide, administered parenterally every 4 - 6 hours or 20 mg of pyridostigmine 4 times orally.

Consideration should be given for pressure control with therapy for accommodation disorder: mydriatics such as tropicamide.

Also see section 4.8.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other nervous system drugs; parasympathomimetics; anticholinesterases

ATC code: N07AA02

Pyridostigmine bromide possesses cholinergic properties; it belongs to cholinesterase inhibitors. Within this group, it has the advantage of a good tolerability, gradual onset of action, constant time-activity profile, and long duration of action as well as gradual attenuation of action. Neostigmine, on the other hand, displays a faster onset of action, higher maximum (peak) concentration and faster attenuation of action.

5.2 Pharmacokinetic properties
The rate and extent of absorption vary greatly among individual patients.

Bioavailability on oral administration of pyridostigmine bromide to healthy subjects was found to vary between 7.6%, 3-4% and 18.9% (on oral administration of 120 mg: Cmax = 40 - 60 μg/L; tmax = 3 - 4 h; 180 - 1440 mg: Cmax = 180 μg/L; tmax = 1.5 h and 120 - 370 mg: Cmax = 20 - 100 μg/L; tmax = 1.5 - 6 h). This low and highly variable bioavailability is ascribed to low absorption.

In patients with myasthenia gravis, it can drop down to 3.3%. Distribution volume on intravenous administration ranges from 1.03 to 1.43 L/kg in healthy subjects and 1.76 L/kg in myasthenia patients. Plasma clearance is very fast, i.e. 0.65 L/kg/hour in healthy subjects and 1.0 to 0.29 L/kg/hour in myasthenia patients. Elimination half-life was found to be 1.74 - 1.51 hours in healthy subjects and 1.05 hours in myasthenia patients. Orally administered pyridostigmine bromide is excreted in a dose-dependent fashion primarily via the kidneys, a fraction of it as unchanged active substance (up to 5-15%) and the rest in the form of inactive metabolites.
Upon oral intake, only a small fraction is absorbed (approx. 22-25%). Excretion of the absorbed fraction of pyridostigmine bromide occurs primarily via the kidneys (75-90%), partly as unchanged active substance and partly in the form of inactive metabolites (in a ratio of 4:1).

5.3 Preclinical safety data
Subcutaneous injection of toxic doses of pyridostigmine bromide to rats caused symptoms such as salivation, convulsions, tremor and respiratory difficulties. On oral administration of toxic doses, rats died from acute respiratory failure. Histology revealed injury to neuromuscular synapses of the diaphragm. Long-term oral administration to rats led to an inhibition of plasma cholinesterase and RBC cholinesterase.

Standard in vitro and in vivo genotoxicity studies gave no indication of a clinically relevant genotoxic potential of pyridostigmine bromide.

Preclinical studies on carcinogenicity of pyridostigmine bromide have not been conducted.

Animal studies on reproductive toxicity have been conducted in rats following oral administration of pyridostigmine bromide. They revealed no effects on the male and female fertility. Embryotoxicity studies revealed increased rates of resorption and delayed ossification in the foetuses at maternally toxic doses. In a peri/postnatal study, the weight gain of the offspring of the treated dams was decreased.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Core
  - Silica colloidal anhydrous
  - Lactose monohydrate
  - Maize starch
  - Povidon K-30
  - Talc
  - Magnesium stearate
- Coating
  - Copovidone
  - sucrose,
  - Calcium carbonate,
  - Talc,
  - Macrogol 6000,
  - Titanium dioxide (E171)
  - Xantham gum
  - Xantham gum
  - Hypromellose
polyvinyl alcohol,
Lecithin (soy),
Sunset yellow FCF aluminium lake (E110),
Yellow iron oxide (E172)
Aspartame (E 951)
Carnauba wax
Printing ink
Shellac (E904),
Black iron oxide (E172),
Propylene glycol
Ammonium hydroxide.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years
HDPE tablet containers:
After first opening: 3 months

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package, in order to protect from moisture.

6.5 Nature and contents of container
HDPE tablet containers with a polypropylene child resistant closure and 2g silica gel canister containing 20, 60, 100, 150 or 250 tablets.
Al/OPA/Al/PVC blisters containing 20, 60, 100, 150 or 250 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Unit 15 Moorcroft
Harrington Road
Hillingdon
UB8 3HD
United Kingdom
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