Translation from Latvian

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Neiromidin® 20 mg tablets
Neiromidin® 5 mg/ml solution for injection
Neiromidin® 15 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance INN: Ipidacrinum.

- Each Neiromidin® 20 mg tablet contains 20 mg of ipidacrine hydrochloride.
- Neiromidin® 5 mg/mL solution for injection: 1 mL solution for injection (1 ampoule) contains 5 mg of ipidacrine hydrochloride (5 mg/mL).
- Neiromidin® 15 mg/mL solution for injection: 1 mL solution for injection (1 ampoule) contains 15 mg of ipidacrine hydrochloride (15 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- Tablets.
White to almost white round flat tablets with bevelled edge.
- Solution for injection.
Transparent colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Peripheral nervous system diseases, such as neuritis, polyneuritis, polyneuropathy, polyradiculoneuropathy, myasthenia and myasthenic syndrome of various etiology;
- Bulbar palsy and paresis;
- Recovery period after organic CNS (Central Nervous System) lesions with motion disorders;
- Complex therapy of demyelinating disease;
- Memory disorders of different origins, such as Alzheimer's disease and other forms of dementia in elderly;
- Intestinal atony.

4.2 Posology and method of administration

Posology

- Neiromidin® 20 mg tablets

Peripheral nervous system diseases, myasthenia and myasthenic syndrome
The recommended dose is 10 to 20 mg 1 - 3 times per day. The course of treatment is 1 - 2 months. If necessary, treatment may be repeated several times at intervals of 1- 2 month.

Memory disorders of different origins, such as Alzheimer's disease and other forms of dementia in elderly
Doses and duration of the treatment should be determined individually. The maximum daily dose may be increased up to 200 mg. The treatment duration is from 1 month and up to 1 year.

Treatment and prophylaxis of intestinal atony
The recommended dose is 20 mg 2 - 3 times daily. The course of treatment is 1 - 2 weeks.

- Neiromidin® 5 mg/mL and 15 mg/mL solution for injection

Peripheral nervous system diseases, myasthenia and myasthenic syndrome
The recommended dose is 5 to 15 mg (1 ampoule of Neiromidin® 5 mg/mL or 15 mg/mL solution for injection) 1-2 times a day, administered as a single intramuscular or subcutaneous injection. The course of treatment is 1 - 2 months. If necessary, treatment may be repeated several times at intervals of 1- 2 month.

Prevention of myasthenic crisis in case of severe neuromuscular transmission disorders
15 – 30 mg (1 – 2 mL of Neiromidin® 15 mg/mL solution for injection) should be administered parenterally over a short period of time. Treatment should be continued with Neiromidin® 20 mg tablets at doses of 20 – 40 mg 5 to 6 times daily.

Memory disorders of different origins, such as Alzheimer's disease and other forms of dementia in elderly
Doses and duration of the treatment should be determined individually. The maximum daily dose may be increased up to 200 mg. The treatment duration is from 1 month and up to 1 year.

Method of administration

- Neiromidin® 20 mg tablets should be administered orally with a glass of water.
- Neiromidin® 5 mg/mL and 15 mg/mL solution for injection should be administered intramuscularly or subcutaneously. Doses and duration of the treatment should be determined individually, according to the severity of the disease.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
Epilepsy;
Extrapyramidal disorders with hyperkinesia;
Angina pectoris, significant bradycardia;
Bronchial asthma;
Intestinal or urinary tract obstruction;
Vestibular disorders;
Exacerbation of gastric or duodenal ulcer;
Pregnancy and lactation.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with a history of gastric and duodenal ulcer, in cases of thyrotoxicosis and cardiovascular diseases as well.
Ipidacrine should be used with caution in patients with a history of respiratory diseases including acute respiratory disease.
Lactose. Each Neiromidin® 20 mg tablet contains 65 mg of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Neiromidin® in combination with CNS depressants increases sedative effect. Neiromidin® activity, as well as the risk of side effects increases, when taken concomitantly with other cholinesterase inhibitors and M-cholinomimetics. In patients with myasthenia gravis the risk of cholinergic crisis enhances, if Neiromidin® is used in combination with other cholinergic agents.
If prior to Neiromidin® administration beta-blockers have been used, the risk of bradycardia may increase.
Cerebrolysin improves mental effects of Neiromidin®.
Alcohol may enhance the risk of undesirable effects.

4.6 Pregnancy and lactation

The medicinal product can increase uterine tone and lead to premature delivery, therefore, ipidacrine is contraindicated during pregnancy.

It is unknown whether ipidacrine is excreted into human breast milk, therefore, it is contraindicated in breast-feeding women.

4.7 Effects on ability to drive and use machines

Neiromidin® may cause sedation. Patients should be advised not to drive or operate machinery if affected.

4.8 Undesirable effects

Like all medicines ipidacrine can cause side effects, although not everybody gets them.
Their frequency is defined using the following conventions: very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).
Neiromidin® is well tolerated. Possible undesirable effects are usually associated with muscarinic cholinoceptors stimulating activity.
Cardiac disorders: common – bradycardia, palpitations.
Nervous system disorders: uncommon, when administering high doses - headache, dizziness, somnolence,
Musculoskeletal and connective tissue disorders: uncommon, when administering high doses - muscle cramps.
General disorders and administration site conditions: uncommon, when administering high doses – weakness.
Respiratory, thoracic and mediastinal disorders: uncommon – increased bronchial secretion.
Gastrointestinal disorders: common – nausea, salivation; uncommon, when administering high doses – vomiting; rare – diarrhoea, epigastric pain.
Skin and subcutaneous tissue disorders: common – sweating; uncommon, when administering high doses – hypersensitivity skin reactions (itching, rash).
Anticholinergic agents, such as atropine, may decrease salivation and bradycardia.
In case of undesirable effects the dose should be decreased or Neiromidin® should be discontinued for a short period of time.

4.9 Overdose

Symptoms: severe overdose may result in cholinergic crisis characterized by bronchospasm, eyes tearing, nystagmus, miosis, vomiting, sweating, bradycardia, hypotension, heart block, arrhythmia, convulsions, unconscious defecation and urination, restlessness, anxiety, agitation, fear, ataxia, convulsions, coma, slurred speech, drowsiness and fatigue. Intensity of the symptoms can be mild.
Treatment: in case of Neiromidin® overdose treatment is symptomatic; anticholinergic agents, such as atropine, trihexyphenidyl, metacin etc.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anticholinesterases . ATC code: N07AA.

Neiromidin® is a reversible cholinesterase inhibitor. It directly stimulates impulse transmission in the CNS and neuromuscular synapses by blocking membrane potassium channels. Neiromidin® enhances not only choline, but also adrenaline, serotonin, histamine and oxytocin effects on smooth muscle.
Neiromidin® main pharmacological effects:
• restores and stimulates neuromuscular transmission;
• restores impulse transmission in the peripheral nervous system due to blockade, caused by various factors, such as trauma, inflammation, local anaesthetics, some antibiotics and potassium chloride exposure, etc.
• enhances smooth muscle contractility affected by the all agonists, excluding potassium chloride;
• moderately and specifically stimulates CNS in combination with some sedative activity;
• improves memory.
There are no adequate studies on the product safety for children.

5.2 Pharmacokinetic properties

Absorption
After oral administration ipidacrine is rapidly absorbed from the gastrointestinal tract. Absorption of ipidacrine mainly takes place in the duodenum and partially in the small intestines. Peak plasma levels after ingesting 10 mg of active substance occur within one hour.

Distribution
Ipidacrine is approximately 40-55% plasma protein bound. Neiromidin® is rapidly and widely distributed in the tissues. When distribution equilibrium is reached, only 2% of ipidacrine is found in the plasma.

Biotransformation
Neiromidin® is metabolised in the liver.

Elimination
Renal excretion is the major route of elimination. Ipidacrine can also be eliminated extrarenally. The elimination half-life of Neiromidin® is about 40 minutes. Neiromidin® is excreted in the urine mainly by tubular secretion and only 1/3 of the dose is excreted by glomerular filtration. 3.7% of the dose is eliminated in the urine unchanged after oral administration, and 34.8% - after parenteral administration.

5.3 Preclinical safety data

Acute toxicity

LD50 mg/kg body weight			
Method of administration	Mice	Rats	Rabbits
Oral	68	62	55
Subcutaneous	52	56	

Acute toxicity data indicate ipidakrine moderate acute toxicity.

Chronic toxicity
Chronic toxicity studies showed ipidakrine safety in case of prolonged use, as well as the fact that undesirable effects, associated with muscarinic cholinoceptors stimulating activity, occur relatively rare and for a short period of time. This allows wide range of dose amounts to achieve desired therapeutic effect.

Carcinogenicity, mutagenicity, teratogenicity, embryotoxicity
Studies did not show ipidakrine carcinogenic, mutagenic, teratogenic, embryotoxic or allergic potential, immunotoxic activity and no adverse impact on the endocrine system as well.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neiromidin® 20 mg tablets: lactose, potato starch, calcium stearate.
Neiromidin® 5 mg/mL solution for injection: 1 M hydrochloric acid (for pH adjustment) and water for injection.
Neiromidin® 15 mg/mL solution for injection: 1 M hydrochloric acid (for pH adjustment) and water for injection.

6.2 Incompatibilities

Neiromidin® 20 mg tablets: not applicable.
Neiromidin® 5 mg/mL and 15 mg/mL solution for injection: in the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Neiromidin® 20 mg tablets: 5 years.
Neiromidin® 5 mg/mL solution for injection: 2 years
Neiromidin® 15 mg/mL solution for injection: 2 years

6.4 Special precautions for storage

Neiromidin® 20 mg tablets:
Do not store above 25 ºC. Protect from light and moisture.
Neiromidin® 5 mg/mL and 15 mg/mL solution for injection:
Do not store above 25 ºC. Protect from light.

6.5 Nature and contents of container

Neiromidin ® 20 mg tablets:
Primary package: 10 tablets in a PVC film and lacquered aluminum foil blister.
Secondary package: 5 blisters (50 tablets) and package leaflet in a carton box.

Neiromidin ® 5 mg/mL solution for injection:
Primary package: one 1 ml neutral glass ampoule (type I) contains 5 mg of ipidakrine hydrochloride.
Secondary package: 10 ampoules rigid PVC tray and package leaflet in a carton box.

Neiromidin ® 15 mg/mL solution for injection:
Primary package: one 1 ml neutral glass ampoule (type I) contains 15 mg of ipidakrine hydrochloride.
Secondary package: 10 ampoules rigid PVC tray and package leaflet in a carton box.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

JSC Olainfarm.
Address: 5, Rupnicu St., Olaine, LV-2114, Latvia.
Phone +371 67013701 • Fax +371 67013777 • e-mail: olainfarm@olainfarm.lv

8. MARKETING AUTHORISATION NUMBERS

Neiromidin® 20 mg tablets: 97-0550
Neiromidin® 5 mg/mL solution for injection: 03-0284
Neiromidin® 15 mg/mL solution for injection: 03-0285

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Neiromidin® 20 mg tablets: 05.11.1997 / 17.03.2003. /12.05.2008.
Neiromidin® 5 mg/mL solution for injection: 11.07.2003/14.07.2008.
Neiromidin® 15 mg/mL solution for injection: 11.07.2003/14.07.2008.

10. DATE OF REVISION OF THE TEXT

18.06.2012.