Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Novistig 0.5 mg/ml + 2.5 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution for injection contains 0.5 mg of glycopyrronium bromide and 2.5 mg neostigmine metilsulfate.

Excipients with known effect:
1 ml of solution contains 3 mg (0.13 mmol) sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution, practically free of visible particles.
Osmolality: 240-340 mOSm/Kg
pH: 3.4-3.8

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reversal of residual non-depolarising (competitive) neuromuscular block.

4.2 Posology and method of administration

Posology
Dosage:
Adults and elderly patients: 1 – 2 ml intravenously over a period of 10 to 30 seconds (equivalent to neostigmine metilsulfate 2.5 mg with Glycopyrronium Bromide 0.5 mg to neostigmine metilsulfate 5 mg with glycopyrronium bromide 1 mg). Alternatively 0.02 ml/kg intravenously over a period of 10 to 30 seconds may be used, (equivalent to neostigmine metilsulfate 0.05 mg/kg with glycopyrronium bromide 0.01 mg/kg).
These doses may be repeated if adequate reversal of neuromuscular blockade is not achieved. Total doses in excess of 2 ml are not recommended as this dose of neostigmine may produce depolarising neuromuscular block.
Paediatric population: 0.02 ml/kg intravenously over a period of 10 to 30 seconds (equivalent to neostigmine metilsulfate 0.05 mg/kg with glycopyrronium bromide 0.01 mg/kg). Alternatively, dilute to 10 ml with water for injections and administer 1 ml per 5 kg bodyweight.
Method of administration: For intravenous injection.

4.3 Contraindications

- Hypersensitivity to the two active substances or to any of the excipients listed in section 6.1
- Novistig 0.5 mg/ml + 2.5 mg/ml solution for injection should not be given to patients with mechanical obstruction of the gastrointestinal or urinary tracts.
- Novistig 0.5 mg/ml + 2.5 mg/ml solution for injection should not be given in conjunction with suxamethonium, as neostigmine potentiates the depolarising myoneural blocking effects of this agent.

4.4 Special warnings and precautions for use

Administer with caution to patients with bronchospasm or severe bradycardia.
Administration of anticholinesterase agents to patients with intestinal anastomoses may produce rupture of the anastomosis or leakage of intestinal contents.
Although combination of glycopyrronium bromide+neostigmine metilsulfate 0.5 mg/ml + 2.5 mg/ml solution for injectionrr has been shown to have less impact on the cardiovascular system than atropine with neostigmine metilsulfate, use with caution

in patients with coronary artery disease, congestive heart failure, cardiac dysrhythmias, hypertension, thyrotoxicosis and cardiac insufficiency.
Use with caution in patients with epilepsy or Parkinson's disease.
This product should be used cautiously in pyrexical patients (especially children) due to inhibition of sweating.
In common with other antimuscarinic drugs caution is advised in patients with prostatic hypertrophy, paralytic ileus, pyloric stenosis and closed angle glaucoma.
Anticholinergic drugs can cause ventricular arrhythmias when administered during inhalation anaesthesia especially in association with the halogenated hydrocarbons.
Quaternary ammonium compounds (like glycopyronium) in large dose have been shown to block the nicotinic muscle end plate receptors. This must be evaluated prior to its administration in patients with myasthenia gravis.
Unlike atropine, glycopyrronium is a quaternary ammonium compound and does not cross the blood-brain barrier. It is therefore less likely to cause postoperative confusion, which is a particular concern in the elderly patients. Compared to atropine, glycopyrrolate has reduced cardiovascular and ocular effects.
Neostigmine metilsulfate: glycopyrronium or alternatively atropine, given before or with neostigmine, prevents bradycardia, excessive salivation, and other muscarinic effects of neostigmine.
This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Neostigmine metilsulfate should not be administered with suxamethonium (See Contra-indications above).
There is increased risk of antimuscarinic side effects in patients taking drugs with antimuscarinic effects such as MAOIs (Monoamine oxidase inhibitors), amantadine, clozapine, tricyclic antidepressants and nefopam.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of glycopyrronium bromide or neostigmine metilsulfate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Glycopyrronium should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.
Anticholinesterase drugs, including neostigmine may cause uterine irritability and induce premature labor when administered to pregnant women near term. Neostigmine metilsulfate should be given to a pregnant woman only if clearly needed.

Breast-feeding
It is unknown whether glycopyrronium bromide or neostigmine metilsulfate are excreted in human milk. However, glycopyrronium bromide (including its metabolites) was excreted in the milk of lactating rats (see section 5.3). The use of glycopyrronium bromide or neostigmine metilsulfate by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Fertility
Reproduction studies and other data in animals do not indicate a concern regarding fertility in either males or females (see section 5.3). In a fertility and early embryonic development study in rats, male rats were treated for 28 days prior to mating and female rats were treated for 14 days prior to mating with intravenous neostigmine metilsulfate (human equivalent doses of 1.6, 4, and 8.1 mcg/kg/day, based on body surface area). No adverse effects were reported at any dose.

4.7 Effects on ability to drive and use machines

Novistig 0.5 mg/ml + 2.5 mg/ml solution for injection may cause the eyesight to become weak, which could interfere with the ability to drive or operate machinery safely.

4.8 Undesirable effects

Adverse events are which have been associated with Glycopyrronium Bromide - Neostigmine Metilsulfate injection are given below, listed by system organ class and frequency.
Undesirable effects are especially likely to occur at treatment onset or at dose increase. The frequency of undesirable effects listed below is defined using the following convention:
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), Not known (cannot be estimated from the available data).

Tabulated list of adverse reactions for glycopyrronium bromide component of Novistig:

System Organ Class	Adverse reaction	Frequency
Immune system disorders	hypersensitivity, angioedema	Not known
Nervous system disorders	Confusion** Dizziness	Not known
Eye disorders	dilatation of the pupils, photophobia, Angle closure glaucoma	Not known
Cardiac disorders	Transient bradycardia*	Not known
Respiratory, thoracic and mediastinal disorders	Bronchial secretion reduced	Not known
Gastrointestinal Disorders	Dry mouth, Constipation, Nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	Flushing, Dry skin Sweating decreased	Not known
Renal and urinary disorders	Micturition urgency Urinary retention	Not known

* Followed by tachycardia, palpitation and arrhythmias
**Particularly in elderly

Tabulated list of adverse reactions for neostigmine metilsufate component of Novistig:

System Organ Class	Adverse reaction	Frequency
Cardiac disorders	Bradycardia, cardiac dysrhythmias	Not known
Respiratory, thoracic and mediastinal disorders	increased oropharyngeal secretions	Not known
Gastrointestinal Disorders	increased gastrointestinal activity	Not known

Glycopyrronium - Neostigmine component of injection can give rise to hypersensitivity, angioedema and anaphylactic reaction. If severe neostigmine - induced muscarinic side effects occur (bradycardia, increased oropharyngeal secretions, decreased cardiac conduction rate, bronchospasm or increased gastrointestinal activity etc.), these may be treated by the intravenous administration of glycopyrronium bromide injection 200 - 600 micrograms (0.2 - 0.6 mg) or atropine 400-1200 micrograms (0.4 - 1.2mg).

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms:
Signs of neostigmine overdosage (including nausea, vomiting, diarrhoea, excessive salivation and sweating, miosis, bradycardia or tachycardia, cardiospasm, inco-ordination, muscle cramps, fasciculation and paralysis, increased oropharyngeal secretions and bronchospasm etc.) may be treated by the administration of glycopyrronium bromide injection 0.2 - 0.6 mg or atropine 0.4 - 1.2 mg. In severe cases, respiratory depression may occur and artificial ventilation may be necessary in such patients.
Signs of glycopyrronium bromide overdosage (tachycardia, ventricular irritability etc.) may be treated by the administration of neostigmine metilsulfate 1.0 mg for each 1.0 mg of glycopyrronium bromide known to have been administered.

Management:
The treatment of overdosage depends on whether signs of anticholinesterase or anticholinergic overdosage is the predominant presenting feature. As glycopyrronium bromide is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature. Centrally acting anticholinesterase drugs such as physostigmine are therefore unnecessary to treat glycopyrronium bromide overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Parasympathomimetics, Anticholinesterases
ATC Code: N07AA51

Mechanism of action:
Glycopyrronium bromide is a quaternary ammonium anticholinergic agent. The quaternary ammonium moiety renders glycopyrronium bromide highly ionised at physiological pH and it thus penetrates the blood brain and placental barriers poorly. Glycopyrronium bromide has a more gradual onset and longer duration of action than atropine. Neostigmine metilsulphate is a quaternary ammonium anticholinesterase.
Combination of glycopyrronium bromide+neostigmine metilsulfate 0.5 mg/ml + 2.5 mg/ml solution for injection is associated with less initial tachycardia and better protection against the subsequent cholinergic effects of neostigmine metilsulfate than a mixture of atropine and neostigmine metilsulfate.
In addition, residual central anticholinergic effects are minimised due to the limited penetration of glycopyrronium bromide into the central nervous system. Administration of glycopyrronium bromide with neostigmine metilsulfate is associated with greater cardiostability than administration of glycopyrronium bromide and neostigmine metilsulfate separately.

5.2 Pharmacokinetic properties

Absorption/Biotransformation:
Glycopyrronium bromide and neostigmine metilsulfate are routinely administered simultaneously to reverse residual non-depolarising (competitive) neuromuscular block. numerous clinical studies, which demonstrate this to be a safe and effective combination, have been published.
Over 90% of the glycopyrronium bromide disappears from serum within 5 minutes following intravenous administration. The pharmacokinetics of neostigmine metilsulfate are described in Martindale. In one study, following intravenous administration, the plasma concentration declined to about 8% of its initial value after 5 minutes with a distribution half-life of less than one minute.

Elimination:
The drug is rapidly excreted into bile with highest concentrations being found 30 to 60 minutes after dosing with some product being detected up to 48 hours after administration. Glycopyrronium bromide is also rapidly excreted into urine with the highest concentrations being found within 3 hours of administration. Over 85% of product is excreted within 48 hours. It has subsequently been confirmed in a single dose pharmacokinetic study using radioimmunological assay procedures that glycopyrronium bromide was rapidly distributed and/or excreted after intravenous administration. The terminal elimination phase was relatively slow with quantifiable plasma levels remaining up to 8 hours after administration. The elimination half-life was 1.7 hours.
Elimination half-life of neostigmine ranged from about 15-30 minutes. Trace amounts of neostigmine metilsulfate could be detected in the plasma after one hour. In a study in non-myasthenic patients, the plasma half-life was 0.89 hours.

5.3 Preclinical safety data

Non-clinical data on glycopyrronium bromide or neostigmine metilsulfate reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Glycopyrronium bromide
Effects attributable to the muscarinic receptor antagonist properties of glycopyrronium bromide included mild to moderate increases in heart rate in dogs, lens opacities in rats and, reversible changes associated with reduced glandular secretions in rats and dogs. Mild irritancy or adaptive changes in the respiratory tract were seen in rats. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.
Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration.

Fertility and pre- and post-natal development were not affected in rats. Glycopyrronium bromide and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Glycopyrronium bromide (including its metabolites) was excreted into the milk of lactating rats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium bromide. Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity at systemic exposures (AUC) of approximately 53-fold higher in mice and 75-fold higher in rats than the maximum recommended dose of 44 micrograms once daily for humans.

Neostigmine metilsulfate
In embryofetal development studies, rats and rabbits were administered neostigmine metilsulfate at human equivalent doses (HED, on a mg/m basis) of 1.6, 4 and 8.1 mcg/kg/day 3.2, 8.1, and 13 mcg/kg/day, respectively, during the period of organogenesis (Gestation Days 6 through 17 for rats and Gestation Days 6 through 18 for rabbits). There was no evidence for a teratogenic effect in rats and rabbits up to HED 8.1 and 13 mcg/kg/day, in the presence of minimal maternal toxicity (tremors, ataxia, and prostration). The studies resulted in exposures in the animals well below predicted exposures in humans.

In a pre- and postnatal development study in rats, neostigmine metilsulfate was administered to pregnant female rats at human equivalent doses (HED) of 1.6, 4 and 8.1 mcg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. There were no adverse effects on physical development, behavior, learning ability, or fertility in the offspring occurred at HED doses up 8.1 mcg/kg/day in the presence of minimal maternal toxicity (tremors, ataxia, and prostration). The studies resulted in exposures in the animals well below predicted exposures in humans.

In a fertility and early embryonic development study in rats, male rats were treated for 28 days prior to mating and female rats were treated for 14 days prior to mating with intravenous neostigmine metilsulfate (human equivalent doses of 1.6, 4, and 8.1 mcg/kg/day, based on body surface area). No adverse effects were reported at any dose.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of neostigmine metilsulfate. Neostigmine metilsulfate was not genotoxic in the in vitro bacterial reverse mutation assay (Ames test), in the in vitro chromosome aberration assay, or the in vivo rat micronucleus assay.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate (E339)
Citric acid anhydrous (E330)
Sodium hydroxide (for pH adjustment) (E524)
Citric acid solution (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
The medicinal product has to be used immediately after first opening.

6.4 Special precautions for storage

Do not freeze.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear colourless glass 2 mL ampoule (filled to 1 ml)
Box of 10 ampoules containing 1 ml of solution for injection.

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

Sintetica GmbH
Albersloher Weg 11
Münster
48155
Germany

8 MARKETING AUTHORISATION NUMBER

PA22835/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th January 2021
Date of last renewal: 29th July 2025

10 DATE OF REVISION OF THE TEXT

January 2025