PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Cholstyq

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.

Excipient with known effect

Each 1 ml of the solution for injection contains 3 mg (0,13 mmol) sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution, practically free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Dosage:

Submission date: May 2024
Implemented: 10 May 2024

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.
- Cholstyq should not be given to patients with mechanical obstruction of the gastrointestinal or urinary tracts.
- Cholstyq should not be given in conjunction with depolarising muscle relaxants, such as 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 asthma, bronchospasm or severe bradycardia, as the neostigmine may aggravate the pathology.

Administration of anticholinesterase agents to patients with intestinal anastomoses may produce rupture of the anastomosis or leakage of intestinal contents.

Cholstyq should be used with caution in patients with coronary artery disease, congestive heart failure, cardiac dysrhythmias, hypertension, hyperthyroidism or thyrotoxicosis and cardiac insufficiency.

Use with caution in patients with epilepsy or Parkinson's disease.

Cholstyq should be used cautiously in pyrexical patients (especially children) due to inhibition of sweating.

In common with other antimuscarinic medicines caution is advised in patients with prostatic hypertrophy, paralytic ileus, pyloric stenosis and closed angle glaucoma.

Cholstyq should be used with caution in patients with hypotension, peptic ulceration or vagotonia.

Anticholinergic medicines can cause ventricular dysrhythmias when administered during inhalation anaesthesia especially in association with the halogenated hydrocarbons.

Quaternary ammonium compounds (like glycopyrronium) in large doses have been shown to block the nicotinic muscle end plate receptors. This must be evaluated prior to its administration in patients with myasthenia gravis. Cholstyq should be used with caution in

patients with myasthenia gravis to avoid provoking a cholinergic crisis with increased muscular weakness.

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. Glycopyrronium bromide glycopyrrolate has reduced cardiovascular and ocular effects.

Neostigmine metilsulfate: glycopyrronium given before or with neostigmine, prevents bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

Cholstyq should be used with caution in elderly patients.

As neostigmine metilsulfate is excreted mainly by the kidneys, caution is advised in cases of impaired renal function.

Cholstyq contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Neostigmine metilsulfate should not be administered with suxamethonium (see section 4.3).

There is increased risk of antimuscarinic side effects in patients taking medicines with antimuscarinic effects such as MAOIs (Monoamine oxidase inhibitors), amantadine, clozapine, tricyclic antidepressants and nefopam.

Aminoglycosides, clindamycin, colistin and the halogenated inhalation anaesthetics possess

neuromuscular blocking activity and may antagonise the effects of neostigmine metilsulfate. These agents must be used with care in conjunction with Cholstyq.

Hypotension and prolonged bradycardia have occurred in patients receiving beta-adrenoceptor blocking agents following administration of neostigmine metilsulfate.

Some antidysrhythmic medicines such as quinidine may antagonize neostigmine metilsulfate action by interfering with neuromuscular transmission.

Administration of methylprednisone to patients receiving neostigmine metilsulfate has exacerbated symptoms and produced profound weakness often necessitating assisted ventilation.

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).

Anticholinesterase medicines, including neostigmine may cause uterine irritability and induce premature labour when administered to pregnant women near term. Neostigmine metilsulfate should be given to a pregnant woman with caution.

Breastfeeding

It is unknown whether glycopyrronium bromide is excreted in human milk. The amount of neostigmine metilsulfate distributed into breastmilk is very small, but breastfed infants need to be monitored. Glycopyrronium bromide (including its metabolites) was excreted in the milk of

lactating rats (see section 5.3). The amount of Cholstyq excreted in breastmilk following a standard single dose is not expected to have any influence on the baby.

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

Cholstyq 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 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.

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

System organ class (MedDRA)	**Adverse event**	**Frequency**
Immune system disorders	Hypersensitivity, severe allergic reaction or pharmacologic	Not known

	idiosyncrasies including anaphylaxis, angioedema	
Nervous system disorders	Confusion and /or excitement**, dizziness, headache, nervousness, drowsiness, weakness, insomnia	Not known
Eye disorders	Blurred vision as a result of dilatation of the pupils, increased ocular tension, 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, loss of taste, bloated feeling	Not known
Skin and subcutaneous tissue disorders	Flushing, dry skin, sweating decreased, urticaria and other dermal manifestations	Not known
Renal and urinary disorders	Micturition urgency, urinary hesitance and retention	Not known
Reproductive system and breast disorders	Impotence, suppression of lactation	Not known

* Followed by tachycardia, palpitation and dysrhythmias

**Particularly in elderly

Tabulated list of adverse reactions for Neostigmine metilsulfate component of Cholstyq:

System organ class (MedDRA)	**Adverse event**	**Frequency**
Cardiac disorders	Bradycardia, cardiac dysrhythmias	Not known
Respiratory, thoracic and mediastinal disorders	Increased oropharyngeal secretions	Not known
Gastrointestinal disorders	Increased gastrointestinal activity, nausea, vomiting, diarrhoea, abdominal cramps, anorexia	Not known
Musculoskeletal and connective tissue disorders	Muscle cramps, fasciculation, weakness	Not known
General disorders and administration site conditions	Salivation	Not known

The 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 – 1,2 mg).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Signs of neostigmine overdosage include nausea, vomiting, eructation, increased peristalsis, diarrhoea, urination and the desire to urinate, excessive salivation and sweating, increased oropharyngeal secretions, flushing, miosis, conjunctival congestion, cilliary spasm, brow ache, nystagmus, restlessness, agitation, fear, excessive dreaming, hallucinations, convulsions, slurred speech, tight chest, wheezing, increased bronchial secretion combined with bronchoconstriction, bradycardia or tachycardia, hypotension, cardiospasm, inco-ordination, muscle cramps, scattered fasciculations and eventually severe weakness and paralysis, convulsions and coma. Paradoxical effects may also occur due to interaction between nicotinic and muscarinic actions. Accordingly there may be tachycardia and hypertension. Death may follow due to cardiac arrest or central respiratory paralysis and pulmonary oedema. In severe cases, respiratory depression may occur and artificial ventilation may be necessary in such patients. Signs of neostigmine overdose may be treated by the administration of glycopyrronium bromide injection 0,2 – 0,6 mg intravenously or atropine sulphate 1 – 2 mg intravenously, intramuscularly or subcutaneously to control the muscarinic effects.

Signs of glycopyrronium bromide overdosage include tachycardia, ventricular irritability and peripheral anticholinergic effects. Signs of glycopyrronium bromide overdose 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 medicines such as physostigmine are therefore unnecessary to treat glycopyrronium bromide overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 5.11 Others

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, like other anticholinergic (antimuscarinic) agents, inhibits the action of acetylcholine on structures innervated by postganglionic, cholinergic nerves and on smooth muscles that respond to acetylcholine, but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretion and controls excessive pharyngeal, tracheal, and bronchial secretions.

Glycopyrronium bromide antagonises muscarinic symptoms (e.g. bronchorrhoea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic medicines such as the anticholinesterases. Glycopyrronium bromide has a more gradual onset and longer duration of action than atropine.

Neostigmine metilsulphate is a quaternary ammonium anticholinesterase.

The combination of glycopyrronium bromide 0,5 mg/ml and neostigmine metilsulfate 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.

With intravenous injection, the onset of action is generally evident within one minute. Over 90 % of the glycopyrronium bromide disappears from serum within 5 minutes following intravenous administration.

The pharmacokinetics of neostigmine metilsulfate are described in literature. 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 medicine is rapidly excreted into bile with the 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.

The elimination half-life of neostigmine ranged from about 15 to 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 embryofoetal 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, behaviour, 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

Citric acid, disodium phosphate dodecahydrate, sodium hydroxide and water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

Cholstyq has to be used immediately after first opening.

6.4 Special precautions for storage

Store at or below 30 °C.

Do not freeze.

Cholstyq has to be used immediately after first opening

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Cholstyq is presented in 2 ml (filled to 1 ml) Type I clear colourless glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

Name of Manufacturer: Sintetica SA

8. REGISTRATION NUMBER

56/5.11/0094.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 May 2022.

10. DATE OF REVISION OF THE TEXT

10 May 2024

NAMIBIA:

Cholstyq: Reg. No.: 22/5.4/0019 NS2