PRESCRIBING INFORMATION
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]PROSTIGMIN®

Neostigmine Bromide Tablets
15 mg tablets for oral use

Anticholinesterases

Bausch Health, Canada Inc.
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PHARMACOLOGY

Neostigmine is an anticholinesterase agent which inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase. The neostigmine-enzyme complex is hydrolyzed at a much slower rate than the acetylcholine-enzyme complex. As a result, acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. It enhances cholinergic action by facilitating the transmission of impulses across neuromuscular junctions. It also has a direct cholinomimetic effect on skeletal muscle. Neostigmine produces generalized cholinergic responses including miosis, increased tonus of intestinal musculature, constriction of bronchi and ureters, bradycardia, and stimulation of secretion by salivary and sweat glands.

Because of its quaternary ammonium structure, moderate doses of neostigmine do not cross the blood-brain barrier to produce CNS effects. Extremely high doses, however, produce CNS stimulation followed by CNS depression, in addition to a depolarizing neuromuscular blockade and may result in respiratory depression, paralysis, and death.

PHARMACOKINETICS

Absorption
Neostigmine bromide is poorly absorbed from the GI tract. Following a single 30-mg oral dose in fasting myasthenia patients, an estimated 1-2 % of the dose was absorbed; peak plasma drug concentrations occurred within 1 to 2 hours, with considerable individual variations. Neostigmine has a variable duration of action in patients with myasthenia gravis, depending on the physical and emotional stress suffered by the patient and the severity of the disease. However, it generally has a more rapid onset than pyridostigmine and a shorter duration of action than pyridostigmine or ambenonium. Effects of neostigmine on peristaltic activity begin 2-4 hours after oral administration.

Distribution
Because of its quaternary ammonium structure, neostigmine would not be expected to cross the placenta in therapeutic doses, nor has the drug been detected in human milk. However, placental transfer of pyridostigmine has been reported after large oral doses, and this possibility should be considered with neostigmine. Neostigmine is 15-25 % bound to serum albumin.

Elimination
Following oral administration of neostigmine, the elimination half-life of the drug averages 52 minutes (range 42-60 minutes).

Neostigmine undergoes hydrolysis by cholinesterases to 3-hydroxyphenyltrimethyl -ammonium (3-OH PTM), which in animals has activity similar to but much weaker than that of neostigmine. Neostigmine is also metabolized by microsomal enzymes in the liver.

Radioisotope studies show the liver as the major site of uptake, although high concentrations of both 3-OH PTM and neostigmine occur in animal heart muscle. Neostigmine and 3-OH PTM are excreted by renal tubular secretion. Unchanged neostigmine and free and conjugated 3-OH PTM have been isolated from urine in animal studies; 3-OH PTM has been identified in human urine. About 80 % of a single intramuscular dose of neostigmine is excreted in urine in 24 hours, approximately 50% as unchanged drug and the remainder as metabolites.

INDICATIONS

PROSTIGMIN is used to improve muscle strength in the symptomatic treatment of myasthenia gravis. PROSTIGMIN may be valuable for long-term oral therapy in patients who can swallow easily. PROSTIGMIN is not effective in patients who are resistant to other anticholinerase drugs.

In **severe myasthenia gravis**, PROSTIGMIN has been used in conjunction with pyridostigmine to provide the benefits of both short- and long-term action; however, because of the possibility of increased toxicity, these combinations should be used only under strict medical supervision.

Ephedrine sulfate and/or potassium chloride have also been given orally with PROSTIGMIN to increase patient response. Approximately one-third of myasthenic patients experience a slight increase in strength when ephedrine is added to anticholinesterase therapy; slightly fewer improvement with potassium.

CONTRAINDICATIONS

PROSTIGMIN should not be administered to:

- patients with a known hypersensitivity to anticholinesterase agents, including neostigmine.

- patients who are hypersensitive to bromides.

- patients with peritonitis, mechanical obstruction of the intestinal or urinary tracts, or doubtful bowel viability.

WARNINGS

PROSTIGMIN should be used with caution in patients with epilepsy, bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), bradycardia, recent coronary occlusion, vagotonia, hyperthyroidism, cardiac arrhythmias or peptic ulcer. Large oral doses of the drug should be avoided in patients with megacolon or decreased gastrointestinal motility. In these patients, the drug may accumulate and result in toxicity when gastrointestinal motility is restored.

PRECAUTIONS

Patients who are hyperreactive to neostigmine experience a severe cholinergic reaction to the drug. Therefore, atropine sulfate injection should always be readily available as an antagonist for the muscarinic effects of neostigmine.

Patients who are hypersensitive to bromides may develop an acneiform rash during neostigmine bromide therapy, which disappears when the drug is discontinued.

Peristalsis induced by neostigmine may disrupt recently completed ileorectal anastomoses if the drug is given after surgery.

When PROSTIGMIN is used to treat myasthenia gravis, it should be kept in mind that individual muscle groups may respond differently to the same dose of an anticholinesterase agent, producing weakness in one muscle group while increasing strength in another. The muscles of the neck and of chewing and swallowing are usually the first muscles weakened by overdosage, followed by the muscles of the shoulder girdle and upper extremities, and finally the pelvic girdle and extraocular and leg muscles.

Vital capacity should be routinely measured whenever dosage is increased in the treatment of myasthenia gravis, so that the dosage of anticholinesterase medication can be adjusted to ensure good respiratory function. Adequate facilities for cardiopulmonary resuscitation, cardiac monitoring, endotracheal intubation, and assisting respiration should be available during dosage adjustment.

When relatively large doses of PROSTIGMIN are taken by myasthenic patients it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of PROSTIGMIN.

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

There is no evidence to suggest that neostigmine bromide has any special effects in the elderly; however, elderly patients may be more susceptible to arrhythmias than the younger adult.

Pregnancy
Few data are available regarding the effects of cholinesterase inhibitors, including neostigmine, on the fetus because of the rarity of maternal conditions requiring the use of these drugs during pregnancy. Transient muscular weakness has occurred in 10 to 20 % of neonates whose mothers received anticholinesterase drugs for the treatment of myasthenia gravis, although similar symptoms have also been reported in infants whose mothers were not treated with these drugs. Anticholinesterase drugs may cause uterine irritability and induce premature labor when given intravenously to pregnant women near term. Use of PROSTIGMIN in pregnant women requires that the possible benefits be weighed against the potential risks.

Nursing Mothers
It is not known whether neostigmine is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from neostigmine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines
Due to miosis and accommodation disorders caused by neostigmine bromide or an inadequate treatment of Myasthenia gravis, PROSTIGMIN may impair visual acuity and consequently the ability to react as well as the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosage Considerations

In the symptomatic treatment of myasthenia gravis, PROSTIGMIN dosage requirements may vary from day to day, according to remissions and exacerbations of the disease and the physical and emotional stress suffered by the patient. Dosage should be adjusted so the patient takes larger doses at times of greatest fatigue (e.g., 30 minutes before meals to assist patients who have difficulty eating).

Complete restoration of muscle strength is rare in myasthenia gravis, and patients should be cautioned not to increase their dose above the maximum response level in an attempt to relieve all symptoms.

Mild exacerbations may be treated under medical supervision by increasing the dose of anticholinesterase medication, as long as the increase produces symptomatic improvement.

When anticholinesterase therapy has been stabilized, patients can be taught to recognize adverse muscarinic effects and modify their dose of PROSTIGMIN accordingly or take atropine if necessary.

Recommended Dose and Dosage Adjustment

Adults
In the initial treatment of myasthenia gravis, PROSTIGMIN should be given orally at a dosage smaller than that required to produce maximum strength (usually 15 mg 3 times daily), and daily dosage should be gradually increased at intervals of 1 or more days. Changes in oral dose may take several days to show results. When a further increase in dosage produces no corresponding increase in muscle strength, dosage should be reduced to the previous level, so that the patient receives the smallest dose necessary to produce maximum strength. An edrophonium test may be helpful in adjusting the dosage.

The usual adult daily maintenance dosage ranges from 15 to 375 mg with an average of 150 mg, but some patients may require 30-40 mg every 2-4 hours.

Adults have been given 25 mg of ephedrine sulfate 2 or 3 times daily and/or 1-2 g of potassium chloride 3 or 4 times daily in conjunction with oral PROSTIGMIN therapy.

Children
The recommended starting daily dosage of PROSTIGMIN for children is 7.5 to 15 mg orally 3-4 times daily; children rarely require more than 45 mg every 2 hours.

Alternatively, an oral pediatric dosage of PROSTIGMIN of 0.333 mg/kg or 10 mg/m^2, 6 times daily has been recommended.

Administration

PROSTIGMIN is administered orally. It reportedly produces fewer adverse muscarinic effects when administered with milk or food.

DRUG OVERDOSAGE AND TREATMENT

Manifestations
PROSTIGMIN overdosage may induce cholinergic crisis, which is characterized by nausea, vomiting, diarrhea, excessive salivation and sweating, increased bronchial secretions, miosis, lacrimation, bradycardia or tachycardia, cardiospasm, bronchospasm, hypotension, incoordination, blurred vision, muscle cramps, weakness, fasciculation, and paralysis. Extremely high dosages may produce CNS symptoms of agitation, fear, or restlessness. Death may result from cardiac arrest or respiratory paralysis and pulmonary edema.

In patients with myasthenia gravis, in whom overdosage is most likely to occur, fasciculation and adverse parasympathomimetic effects may be mild or absent, making cholinergic crisis difficult to distinguish from myasthenic crisis. The time of onset of weakness may indicate whether the crisis is the result of overdosage or underdosage of (or resistance to) anticholinesterase drugs. Weakness that begins **approximately 1 hour** after drug administration suggests **overdosage**, while weakness occurring **3 or more hours** after drug administration is

more likely to be due to **underdosage or resistance**. Edrophonium can be used to distinguish cholinergic crisis from myasthenic crisis.

Treatment
In the treatment of neostigmine overdosage, maintaining adequate respiration is of primary importance. Tracheostomy, bronchial aspiration, and postural drainage may be required to maintain an adequate airway; respiration can be assisted mechanically or with oxygen, if necessary. PROSTIGMIN should be discontinued immediately and 1 to 4 mg of atropine sulfate administered intravenously. Additional doses of atropine may be given every 5 to 30 minutes as needed to control muscarinic symptoms. Atropine overdosage should be avoided, as tenacious secretions and bronchial plugs may result. It should be kept in mind that, unlike muscarinic effects, the skeletal muscle effects and consequent respiratory paralysis which can occur following PROSTIGMIN overdosage are not alleviated by atropine.

ADVERSE EVENTS

Side-effects and adverse reactions may include nausea and vomiting, increased salivation, diarrhoea and abdominal cramps.

DRUG INTERACTIONS

Atropine antagonizes the muscarinic effects of PROSTIGMIN, and this interaction is utilized to counteract the muscarinic symptoms of neostigmine toxicity.

Neostigmine does not antagonize, and in fact may prolong the phase I block of depolarizing muscle relaxants such as succinylcholine or decamethonium.

Anticholinesterase agents are sometimes effective in reversing neuromuscular block induced by aminoglycoside antibiotics. However, aminoglycoside antibiotics, local and some general anesthetics, antiarrhythmic agents, and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis, and the dose of neostigmine may have to be increased accordingly. Theoretically, drugs such as dexpanthenol, which are converted to pantothenic acid in vivo, may have additive effects with PROSTIGMIN by increasing production of acetylcholine.

In severe myasthenia gravis, neostigmine has been used in combination with pyridostigmine to provide the benefits of short and long-term activity; because of the possibility of reduced intestinal motility and increased toxicity, this combination should be used only under strict medical supervision.

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Each white, round, flat-faced tablet with beveled edges; “PROSTIGMIN” and “15” engraved on the perimeter of one face, partially scored and engraved “V” on the other contains neostigmine bromide 15 mg. Also contains lactose, gelatin, sugar, starch.

Gluten-, paraben-, sodium-, sulfite- and tartrazine-free.

Supplied in bottles of 100 tablets.

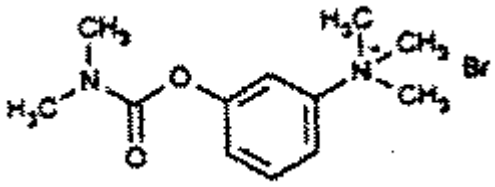
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Neostigmine bromide

Chemical Name: Benzenaminium,3-[[(dimethylamino)carbonyl] oxy]-N, N, N-trimethyl-, bromide
- (m-Hydroxyphenyl) trimethylammonium bromide dimethylcarbamate

Structural Formula:



Molecular Formula: $C_{13}H_{19}BrN_20_2$

Molecular Weight: 303.20 g/mol

Physicochemical Properties

Description: Neostigmine bromide occurs as hygroscopic, odorless, colorless crystals or as a white crystalline powder.

Solubility: Soluble 1 in 0.5 of water and 1 in 8 of alcohol, freely soluble in chloroform; practically insoluble in ether.

Storage Recommendations
Store tablets at controlled room temperature at 15-30ºC. Keep in airtight containers. Protect from light. Keep from sight and reach of children.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPROSTIGMIN®
Neostigmine Bromide Tablets

Read this carefully before you start receiving **PROSTIGMIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PROSTIGMIN**.

What is PROSTIGMIN used for?
PROSTIGMIN is used to treat patients with myasthenia gravis. This is a disease in which the muscles are weak and tire easily.

How does PROSTIGMIN work?
PROSTIGMIN blocks the action of an enzyme in the body which "switches off" nerve impulses to muscles. By stopping this enzyme from working, PROSTIGMIN can increase muscle strength, but only in certain conditions.

What are the ingredients in PROSTIGMIN?
Medicinal ingredients: neostigmine bromide
Non-medicinal ingredients: gelatin, lactose, starch and sugar.

PROSTIGMIN comes in the following dosage forms:
Tablets: 15 mg

Do not use PROSTIGMIN if:
- you are allergic to neostigmine, to bromides or to any of the other ingredients in this medicine;
- you were told you are allergic to drugs called "cholinesterase inhibitors";
- you have peritonitis, which is inflammation of the tissue that lines the abdomen;
- you have a blockage in your intestine, which may cause vomiting, abdominal pain and swelling;
- you have a blockage in your urinary tract. This may make it difficult to urinate.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive PROSTIGMIN. Talk about any health conditions or problems you may have, including if you:
- suffer from asthma;
- have chronic obstructive pulmonary disease (COPD);
- have a stomach ulcer;
- suffer from epilepsy (fits);
- suffer from Parkinson's disease;
- have vagotonia. This is an irritability of the vagus nerve which may cause excessive contractions of the bowels;

- have an overactive thyroid gland. This is called hyperthyroidism;
- have peptic ulcers, which are sores in the lining of the stomach or intestine;
- have recently had a coronary occlusion. This is a blockage of a blood vessel around the heart;
- have an arrhythmia (an irregular heart rate) or bradycardia (a slow heart rate);
- have a widening of the colon. This condition is called megacolon;
- have decreased gastrointestinal motility. This is a condition where the intestinal contractions are abnormal which slows digestion.
- you have recently had surgery;
- you have one of the following rare hereditary disease:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  This is because PROSTIGMIN contains lactose.
- are pregnant;
- are breast-feeding. It is not known if PROSTIGMIN passes into breastmilk. It's possible that it could harm your nursing infant. Your healthcare professional will help you decided whether you should stop nursing your baby during your treatment.

Other warnings you should know about:

Driving and using machines: PROSTIGMIN can affect how you focus your vision on an object. Before your perform tasks which require special attention, wait until you know how you respond to PROSTIGMIN.

Tests: You will have lung tests done regularly while you are taking PROSTIGMIN.

Other treatment: You may need to take other medicines during your treatment with PROSTIGMIN. These medicines might include:
- atropine, ephedrine and / or potassium chloride,
- pyridostigmine. If, after taking PROSTIGMIN and pyridostigmine, you experience side effects like stomach cramps, nausea or vomiting, tell your healthcare professional right away.

Tell your healthcare professional right away if you have sudden weakness in your neck muscles, or have problems chewing or swallowing. These could be signs that your dose of PROSTIGMIN needs to be adjusted.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PROSTIGMIN:
- anaesthetics, which are used to numb an area of the body or put a patient to sleep;
- a medicine used to treat a low heart rate called atropine;
- medicines used to treat bacterial infections called aminoglycosides;

- medicines to prevent and treat arrhythmias.

How to take PROSTIGMIN:
- Take PROSTIGMIN exactly as your healthcare professional has told you. Contact your doctor, nurse or pharmacist if you are not sure.
- Swallow tablet (s) with milk or take with food.

Usual dose:
Adults and children: The dose of PROSTIGMIN and how often it is taken will vary person to person. Your healthcare professional will tell you how much PROSTIGMIN to take and when to take it. Contact your doctor, nurse or pharmacist if you have questions.

Overdose:
Some of the signs of an overdose could be:
- stomach cramps
- diarrhea
- nausea
- vomiting
- increased production of saliva.

If you think you, or a person you are caring for, have taken too much PROSTIGMIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you think that you may have missed a dose, take it as soon as you remember. If it is nearly time for the next dose, wait until the next dose and go back to your regular dosing schedule. Do not take a double dose.

What are possible side effects from using PROSTIGMIN?
These are not all the possible side effects you may have when taking PROSTIGMIN. If you experience any side effects not listed here, tell your healthcare professional.

- nausea
- vomiting
- abdominal cramps
- increased production of saliva
- diarrhea

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 15 - 30ºC.
- Keep in airtight containers.
- Protect from light.
- The product should not be used after the expiry date printed on the label.
- Keep out of reach and sight of children.

If you want more information about PROSTIGMIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.bauschhealth.ca), or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

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