ANTIMYASTHENICS (Systemic)

Introduction

Revised: 09/30/91

Interim revision: 07/18/94

This monograph includes information on the following:1) Ambenonium b; 2**) Neostigmine; 3**) Pyridostigmine.

VA CLASSIFICATION (Primary)¾AU300

Commonly used brand name(s):Mestinon3; Mestinon Timespans3; Mestinon-SR3; Mytelase Caplets1; Prostigmin2; Regonol3.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

b Not commercially available in Canada.

Category

Note: Cholinergic (cholinesterase inhibitor) is the basic category; the other categories are specific categories of use.Cholinergic (cholinesterase inhibitor)¾Ambenonium; Neostigmine; Pyridostigmine 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 34; Antimyasthenic¾ Ambenonium; 18, 19 Neostigmine; 1, 10, 11, 12 Pyridostigmine. 8, 9, 16, 19; Antidote (to nondepolarizing neuromuscular block)¾Neostigmine (parenteral only) 1, 10, 11, 12 ; Pyridostigmine (parenteral only) 8, 9, 16, 19; Diagnostic aid (myasthenia gravis)¾Neostigmine (parenteral only).

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Myasthenia gravis (treatment)¾Ambenonium 18 , neostigmine 10, 11, 12, 13, 14, 34 , and pyridostigmine 8, 9, 15, 16, 17 are indicated in the treatment of myasthenia gravis. Ambenonium is used less commonly than neostigmine or pyridostigmine but may be preferred in patients hypersensitive to the bromide ion 1, 20.

Oral neostigmine or pyridostigmine is most useful in prolonged therapy where no difficulty in swallowing is present 13.

In acute myasthenic crisis where difficulty in breathing and swallowing is present, the parenteral dosage form should be used and the patient transferred to the oral dosage form as soon as tolerated 8, 13.

In the treatment of myasthenia gravis, other treatment (such as respiratory therapy and control of secondary infection) must be administered concurrently with the antimyasthenic.

Ileus, gastrointestinal, postoperative (prophylaxis and treatment); or

Urinary retention, postoperative (prophylaxis and treatment)¾Parenteral neostigmine is indicated in the treatment of postoperative nonobstructive urinary retention. Although it is not commonly used, parenteral neostigmine may also be indicated for the prevention and treatment of postoperative gastrointestinal ileus and prevention of postoperative urinary retention. 10, 11, 12, 14, 34

Neuromuscular blockade, nondepolarizing (treatment)¾Parenteral neostigmine 10, 11, 12, 14, 16, 34 and pyridostigmine 8, 9 are indicated as antidotes to tubocurarine and other nondepolarizing neuromuscular blocking agents.

[Myasthenia gravis (diagnosis)] *¾Parenteral neostigmine has been used as a diagnostic test for myasthenia gravis. Although edrophonium is usually considered the agent of first choice because of its rapid onset and brief duration of action, neostigmine is sometimes used to confirm the edrophonium response. 40, 44

Unaccepted

Although parenteral neostigmine has been used as a screening test for pregnancy and in the treatment of delayed menstruation, these uses of neostigmine are obsolete.

* Not included in Canadian product labeling.

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Pharmacology/Pharmacokinetics

See Table 1.

Physicochemical characteristics:

Molecular weight¾Neostigmine bromide: 303.20 13

Neostigmine methylsulfate: 334.39 10, 11, 12, 34

Pyridostigmine bromide: 261.12

Other characteristics¾Neostigmine methylsulfate injection: pH approximately 5.9 12, 14.

Pyridostigmine bromide injection: pH approximately 5.0 8, 9, 16.

Mechanism of action/Effect:

Cholinergic (cholinesterase inhibitor)¾ Antimyasthenics inhibit destruction of acetylcholine by acetylcholinesterase, thereby facilitating transmission of impulses across the myoneural junction 1, 8, 9, 10, 11, 12, 13, 14, 16, 17, 34.

Cholinergic responses produced are miosis, bradycardia, increased tonus of intestinal and skeletal muscle, constriction of bronchi and ureters, and stimulation of secretion by salivary and sweat glands 21.

In addition, these medications have a direct cholinomimetic effect on skeletal muscle 10, 11, 12, 13, 14, 34.

Neostigmine may also act on autonomic ganglion cells and neurons of the central nervous system (CNS) 10, 11, 12, 13, 14, 34.

Neostigmine prevents or relieves postoperative distention by stimulating gastric motility and increasing gastric tone, which probably represents a combination of actions at the ganglion cells of Auerbach's plexus and at the muscle fibers as a result of the preservation of acetylcholine released by the cholinergic preganglionic and postganglionic fibers, respectively 21, 22.

Neostigmine prevents or relieves urinary retention by increasing the tone of the detrusor muscle of the urinary bladder to produce contractions strong enough to initiate micturition 21, 22.

Antimyasthenic¾ Muscle strength and response to repetitive nerve stimulation is increased as a result of these medications enhancing the peak effect and prolonging the duration of action of acetylcholine at the motor end plate 19.

Antidote (to nondepolarizing neuromuscular block)¾ Since nondepolarizing neuromuscular blocking agents combine reversibly with the receptors, preventing access of acetylcholine, antagonism can be overcome by increasing the amount of agonist at the receptors; therefore, muscle paralysis induced by nondepolarizing neuromuscular blocking agents is reversed by neostigmine or pyridostigmine, which increases concentration of acetylcholine at the receptors 23, 24.

Diagnostic aid (myasthenia gravis)¾ By prolonging the duration of action of acetylcholine at the motor end plate, neostigmine increases muscle strength in patients with myasthenia gravis, whereas patients with other disorders develop either no increase in muscle strength or even a slight weakness and possibly fasciculations. 19, 24

Absorption: 1, 6

Oral¾Poorly absorbed from the gastrointestinal tract 21, 32.

Parenteral¾Intramuscular: Neostigmine is rapidly absorbed 10, 11, 12.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to bromides may be sensitive to neostigmine (oral) or pyridostigmine also 20.

Pregnancy/Reproduction

Pregnancy¾Problems with cholinesterase inhibitors in the human fetus have not been documented; however, transient muscular weakness has occurred in about 20% of infants born to mothers who received these medications during pregnancy 2.

For neostigmine: Studies with neostigmine have not been done in either animals or humans 10, 11, 12, 13, 34.

FDA Pregnancy Category C 10, 11, 12, 13, 34.
Labor and delivery¾Anticholinesterase agents may cause uterine irritability and induce premature labor when given intravenously to pregnant women near term 10, 11, 12, 13, 34.

Breast-feeding

Pyridostigmine is distributed into breast milk in concentrations of 36 to 113% of maternal plasma concentrations 35.

It is not known whether ambenonium and neostigmine are distributed into breast milk 1, 2, 10, 11, 12, 13, 34.

However, problems in humans have not been documented.

Pediatrics

Appropriate studies on the relationship of age to the effects of cholinesterase inhibitors have not been performed in the pediatric population. However, no pediatrics-specific problems have been documented to date.

Geriatrics

Extensive studies with cholinesterase inhibitors have not been performed in the geriatric population. However, in one study in which 14 out of 32 adult patients were over 60 years of age, the duration of antagonism of neuromuscular blockade by neostigmine and pyridostigmine in the elderly group was prolonged compared to younger patients. 4, 5

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Aminoglycosides, systemic 8, 10, 11, 12, 13, 19, 20, 34, 37, 38, 39 or

Anesthetics, hydrocarbon inhalation 8, 10, 11, 12, 13, 19, 20, 32, 34, 39 , such as:

Chloroform

Cyclopropane

Enflurane

Halothane

Methoxyflurane 37

Trichloroethylene or

Anesthetics, parenteral-local 10, 11, 12, 13, 19, 32, 34 , large doses or

Capreomycin or

Lidocaine, intravenous or

Lincomycins 20, 38 or

Polymyxins 8, 19, 20, 32, 37, 38, 39 , such as colistimethate, colistin, and polymyxin B or

Quinine 8, 20, 39

(neuromuscular blocking action of these medications may antagonize the effect of antimyasthenics on skeletal muscle; temporary dosage adjustments of antimyasthenics may be necessary to control symptoms of myasthenia gravis during and following concurrent use)

(antimyasthenics, especially in large doses, may decrease the neuromuscular blocking activity of these medications)

Anesthetics, local 10, 11, 12, 13, 19, 32 , ester-derivative

(antimyasthenic agent-induced inhibition of plasma cholinesterase activity reduces the metabolism of these anesthetics, leading to increased risk of toxicity; it is recommended that local anesthetics that are not ester derivatives be used instead)

Anticholinergic agents, 1, 18 especially atropine and related compounds

(atropine may be used to reduce or prevent the muscarinic effects of antimyasthenics; however, routine concurrent use is not recommended since the muscarinic effects may be the first signs of overdose and masking them with atropine may prevent early recognition of cholinergic crisis 1, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17)

(concurrent use of anticholinergics with antimyasthenics may further reduce intestinal motility; therefore, caution is recommended 13)

>> Cholinesterase inhibitors, other, including demecarium, echothiophate, and isoflurophate, and possibly topical malathion

(concurrent use of other cholinesterase inhibitors with antimyasthenics is not recommended except under strict medical supervision because of the possibility of additive toxicity; caution may also be warranted with topical application of malathion if excessive quantities are used)

Edrophonium

(caution is recommended in administering edrophonium to patients with symptoms of myasthenic weakness who are also receiving antimyasthenics, since symptoms of cholinergic crisis [overdosage] may be similar to those occurring with myasthenic crisis [underdosage] and the patient's condition may be worsened by use of edrophonium)

>> Guanadrel or

>> Guanethidine 39 or

>> Mecamylamine 1, 18, 39 or

>> Trimethaphan

(these ganglionic-blocking medications may antagonize the effects of antimyasthenics when used concurrently, leading to increased muscle weakness, respiratory weakness, and/or difficulty in swallowing; the possibility should be considered that the antihypertensive effects of the ganglionic-blocking medication may also be decreased during concurrent use)

Neuromuscular blocking agents 10, 11, 12, 20, 31

(phase I block of depolarizing neuromuscular blocking agents such as succinylcholine may be prolonged when used concurrently with neostigmine or pyridostigmine; 10, 11, 12 however, if a depolarizing neuromuscular blocking agent has been used over a prolonged period of time and the depolarization block has changed to a nondepolarization block, neostigmine or pyridostigmine may reverse the nondepolarization block)

(effects of nondepolarizing neuromuscular blocking agents are antagonized by parenteral neostigmine or pyridostigmine; this interaction may be used to therapeutic advantage to reverse muscle relaxation following surgery 32)

(neuromuscular blockade antagonizes the effect of antimyasthenics on skeletal muscle; temporary dosage adjustments of antimyasthenics may be required to control symptoms of myasthenia gravis following use of a neuromuscular blocking agent)

>> Procainamide 8, 19, 20, 24, 37, 38, 39 or

Quinidine 8, 20, 24, 37, 38, 39

(neuromuscular blocking activity and/or secondary anticholinergic effects of these medications may antagonize the action of antimyasthenics; caution is recommended during concurrent use in patients with myasthenia gravis 32)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist

Asthma, bronchial 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 34, 37

(increase in bronchial secretions and other respiratory effects of antimyasthenics may aggravate condition)

Atelectasis, postoperative, or

Pneumonia

(may be exacerbated)

Cardiac dysrhythmias, 8, 9, 10, 11, 12, 13, 15, 16, 34 especially bradycardia 11, 12, 13, 34 and atrioventricular (AV) block

(increased risk of cardiac arrhythmias)

>> Intestinal or urinary tract obstruction, mechanical 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 34, 37

(may be exacerbated)

Sensitivity to any of these medications 8, 9, 10, 11, 12, 13, 15, 16, 34 or to bromides 37

>> Urinary tract infections

(increase in urinary bladder muscle tone may aggravate symptoms)

>> (Caution is also recommended in the postsurgical patient because antimyasthenics may exacerbate respiratory problems caused by postoperative pain, sedation, retained secretions, or atelectasis. In the myasthenic patient, if a postoperative respiratory problem cannot be attributed to myasthenia gravis alone, mechanical ventilation is recommended.)

Side/Adverse Effects

Note: Most common adverse reactions to cholinesterase inhibitors are caused by excessive cholinergic stimulation. These include both muscarinic and nicotinic effects. 6, 8, 9, 14, 15, 16, 17, 20

Ambenonium produces fewer muscarinic side/adverse effects than neostigmine but more than pyridostigmine 19.

Neostigmine produces more severe muscarinic side effects than ambenonium or pyridostigmine 17, 18, 20, 32, 38.

Pyridostigmine may produce a significantly lower degree and incidence of bradycardia, salivation, and gastrointestinal stimulation than neostigmine 9, 16.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence rare

Sensitivity to bromide ion of neostigmine or pyridostigmine 8, 9, 10, 15, 16, 17, 34 (skin rash); thrombophlebitis (redness, swelling, or pain at injection site)¾for pyridostigmine injection only 8, 9, 16

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Muscarinic effects 8, 9, 33, 37, 39 (diarrhea; increased sweating; increased watering of mouth; nausea or vomiting; stomach cramps or pain)

Incidence less frequent

Muscarinic effects 8, 9, 33, 37, 39 (frequent urge to urinate; increase in bronchial secretions; unusually small pupils; unusual watering of eyes)

Overdose

For specific information on the agents used in the management of antimyasthenics overdose, see: Atropine in Anticholinergics/Antispasmodics (Systemic) monograph.

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing .

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical signifiance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Acute and chronic

CNS effects 8, 33 (clumsiness or unsteadiness; confusion; difficulty in breathing; seizures; slurred speech; unusual irritability, nervousness, restlessness, or fear); muscarinic effects 8 (blurred vision;

severe diarrhea; excessive increase in bronchial secretions or salivation; severe vomiting; shortness of breath; troubled breathing; wheezing, or tightness in chest; slow heartbeat; severe stomach cramps or pain; unusual tiredness or weakness); nicotinic effects 8 (increasing muscle weakness or paralysis, especially in the arms, neck, shoulders, and tongue; muscle cramps or twitching)

Note: Breathing problems may also be caused by atelectasis.

Unusual tiredness or weakness may also be caused by hypokalemia resulting from severe diarrhea and vomiting.

In the myasthenic patient, increased muscle weakness may be caused by underdosage or resistance instead of by overdosage.

Note: Overdosage may induce cholinergic crisis, 10, 11, 12, 13, 15, 16, 17, 18, 34 which is characterized by nicotinic effects in addition to intensified muscarinic effects 20.

In patients with myasthenia gravis or in the postoperative patient, cholinergic crisis may be difficult to distinguish from myasthenic crisis on a symptomatic basis because the principal symptom common to both is generalized muscle weakness 10, 11, 12, 13, 14, 16, 17, 34.

The time of onset of weakness may help determine whether the crisis is caused by overdosage or underdosage (or resistance). Weakness beginning about 1 hour after administration of antimyasthenic is probably overdosage while that occurring 3 or more hours after administration is probably underdosage or resistance.

If a differential diagnosis cannot be made on the basis of signs and symptoms, edrophonium may be used to distinguish cholinergic crisis from myasthenic crisis; 8, 12, 13, 14, 15, 16, 17, 34, 37 however, caution is recommended because edrophonium will cause increased oropharyngeal secretions and further weakness in muscles of respiration in a cholinergic crisis. This may be especially critical in the postoperative patient.

Treatment of overdose

Recommended treatment for cholinergic crisis¾ Prompt discontinuation of antimyasthenic 8, 17, 18, 39.

Specific treatment¾Use of intavenous atropine sulfate 10, 14, 18, 37, 39 to counteract muscarinic effects 14.

Supportive care¾May include establishment of endotracheal tube, if necessary 8, 37, 39.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Antimyasthenics (Systemic).

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to antimyasthenics or to bromides

Pregnancy¾Possible transient muscle weakness in newborns whose mothers received antimyasthenics during pregnancy

Use in the elderly¾In one study in a limited number of patients, duration of antagonism of neuromuscular blockade by neostigmine and pyridostigmine was prolonged

Other medications, especially other cholinesterase inhibitors, guanadrel, guanethidine, mecamylamine, procainamide, or trimethaphan

Other medical problems, especially intestinal or urinary tract blockage or, urinary tract infection

Proper use of this medication

Taking with food or milk to decrease possibility of side effects

>> Importance of not taking more medication than the amount prescribed

For use in myasthenia gravis: Keeping daily record of dosing and effects on condition during initial therapy

Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses

>> Proper dosing

>> Proper storage

Side/adverse effects

Signs of potential side effects, especially thrombophlebitis at injection site (for pyridostigmine only), and sensitivity

General Dosing Information

In myasthenia gravis, the dosage must be individualized according to the severity of the disease and the response of the patient 18, 19.

To assist the physician in arranging an optimum therapeutic regimen in the treatment of myasthenia gravis, patients should keep a daily record of their condition 13, 20.

Therapy in myasthenia gravis is frequently required day and night. Larger portions of the total daily dose may be taken at times of greater fatigue such as in the afternoons or at mealtimes 13.

Following prolonged therapy, myasthenic patients may become refractory to these medications. Responsiveness may be restored, especially when the resistance may have been caused by overdosage, by reducing the dosage or discontinuing the medication for a few days. 20, 32

For parenteral dosage forms only

Patients should be closely observed for cholinergic reactions, especially when neostigmine or pyridostigmine is administered intravenously.

Atropine injection and antishock medication should always be readily available because of the possibility of hypersensitivity reactions 8, 9, 10, 11, 12, 14, 16, 34.

When large doses of parenteral neostigmine or pyridostigmine are administered, as during reversal of muscle relaxants, prior or concurrent administration of atropine injection is recommended to counteract the muscarinic side effects 8, 10, 12, 14, 16, 34.

Diet/Nutrition

Administration of oral forms of these medications with food or milk may decrease the muscarinic side effects by slowing down absorption of the medication and reducing serum peaks 20, 39.

AMBENONIUM

Summary of Differences

Pharmacology/pharmacokinetics¾ Has longer duration of action than neostigmine 18, 37 or pyridostigmine 37.

Side/adverse effects¾ Produces fewer muscarinic side effects than neostigmine, 18 but more than pyridostigmine.

Oral Dosage Forms

AMBENONIUM CHLORIDE TABLETS

Usual adult and adolescent dose

Antimyasthenic¾Oral, initially 5 mg three or four times a day 18, 19, 37 , the dosage being adjusted as required at intervals of one to two days to avoid accumulation of medication and overdosage 19.

Note: When doses of more than 200 mg per day are administered, the patient should be closely observed for cholinergic reactions 18, 19.

Usual pediatric dose

Antimyasthenic¾ Oral, initially 300 mcg (0.3 mg) per kg of body weight or 10 mg per square meter of body surface per day (divided into three or four doses), the dosage being increased, if necessary, to 1.5

mg per kg of body weight or 50 mg per square meter of body surface per day (divided into three or four doses) 26, 37.

Usual geriatric dose

See Usual adult and adolescent dose .

Strength(s) usually available

U.S.¾10 mg (Rx)[Mytelase Caplets (scored) (acacia) (dibasic calcium phosphate) (gelatin) (lactose) (magnesium stearate) (starch) (and sucrose)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

NEOSTIGMINE

Summary of Differences

Category: Parenteral neostigmine¾ Also indicated as an antidote (to nondepolarizing neuromuscular block) and a diagnostic aid (myasthenia gravis).

Indications: Parenteral neostigmine¾ Also indicated in the treatment of postoperative nonobstructive urinary retention.
May also be indicated for prevention and treatment of postoperative gastrointestinal ileus and prevention of postoperative urinary retention.

Pharmacology/pharmacokinetics¾ Has shorter duration of action than ambenonium.

Precautions: Cross-sensitivity and/or related problems¾ Oral neostigmine contains bromide ion to which some patients may be sensitive.

Side/adverse effects¾ Produces more severe muscarinic side effects than ambenonium or pyridostigmine 17, 18, 20, 32, 38.

Additional Dosing Information

See also General Dosing Information .

Generally, 15 mg of neostigmine bromide administered orally is equivalent to 500 mcg (0.5 mg) of neostigmine methylsulfate administered parenterally 1, 13.
For oral dosage forms only
· Neostigmine is poorly absorbed from the gastrointestinal tract following oral administration; therefore, much larger doses are required for oral than for parenteral use 13, 21.

· Large oral doses should be avoided in conditions where there may be an increased absorption rate from the intestinal tract, in order to avoid possible toxicity 13, 21.

For parenteral dosage forms only: When used as an antidote to nondepolarizing neuromuscular block

· It is recommended that the exact dose required be titrated, using a peripheral nerve stimulator device 1, 10, 11, 12, 34.

· Unless tachycardia is present, atropine (0.6 to 1 mg) should be administered concomitantly or several minutes before neostigmine to prevent bradycardia 1, 10, 11, 12, 34.

· In the presence of bradycardia, the pulse rate should be increased to about 80 per minute with atropine prior to administration of neostigmine 1, 10, 11, 12, 34.

When used as a diagnostic aid (myasthenia gravis)

· Significant improvement of muscle weakness occurring within several minutes to 1 hour following administration of neostigmine usually indicates myasthenia gravis. However, diagnosis also should include clinical and electromyographic (EMG) evaluation.

Oral Dosage Forms

NEOSTIGMINE BROMIDE TABLETS USP

Usual adult and adolescent dose

Antimyasthenic¾Initial¾Oral, 15 mg every three to four hours, the dose and frequency of administration being adjusted as necessary 19, 37.

Maintenance¾Oral, 150 mg administered over a twenty-four-hour period, the intervals between doses being determined by response of the patient 13, 19.

Note: The twenty-four-hour maintenance dose is highly variable among individuals.

Usual pediatric dose

Antimyasthenic¾Oral, 2 mg per kg of body weight or 60 mg per square meter of body surface per day, divided into six to eight doses 19, 26, 37.

Usual geriatric dose

See Usual adult and adolescent dose .

Strength(s) usually available

U.S.¾15 mg (Rx)[Prostigmin 12, 13 (scored) (lactose)] [Generic]

Canada¾15 mg (Rx)[Prostigmin (scored) (lactose)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

NEOSTIGMINE METHYLSULFATE INJECTION USP

Usual adult and adolescent dose

Antimyasthenic¾Intramuscular or subcutaneous, 500 mcg (0.5); subsequent doses should be based on the patient's response 10, 11, 12, 37.

Antidote (to nondepolarizing neuromuscular block)¾Intravenous, 500 mcg (0.5) to 2 mg administered slowly 10, 11, 12, 14 , repeated as required up to a total dose of 5 mg 10, 11, 12.

Note: Subsequent doses may be less than 500 mcg (0.5mg).

When neostigmine is administered intravenously, it is recommended that 600 mcg (0.6) to 1.2 mg of atropine sulfate be administered intravenously prior to or concurrently with neostigmine to counteract its muscarinic side effects 10, 11, 12, 14, 34.

Diagnostic aid (myasthenia gravis) *¾Intramuscular or subcutaneous, 1.5 mg administered simultaneously with 600 mcg (0.6 mg) of atropine

Note: Significant improvement of muscle weakness occurring within several minutes to one hour indicates myasthenia gravis.

Prevention of postoperative distention or urinary retention¾Intramuscular or subcutaneous, 250 mcg (0.25 mg) immediately following surgery, repeated every four to six hours for two or three days 10, 11, 12.

Treatment of postoperative distention¾Intramuscular or subcutaneous, 500 mcg (0.5 mg) as needed 10, 11, 12.

Treatment of urinary retention¾Intramuscular or subcutaneous, 500 mcg (0.5 mg); dose repeated every three hours for at least five doses after patient has voided or the bladder has been emptied 10, 11, 12, 14.

Note: If urination does not occur within one hour following the initial 500-mcg (0.5-mg) dose, the patient should be catheterized 10, 11, 12, 14.

Usual pediatric dose

Antimyasthenic¾Intramuscular or subcutaneous, 10 to 40 mcg (0.01 to 0.04 mg) per kg of body weight every two to three hours 19, 37.

Note: A dose of 10 mcg (0.01 mg) of atropine per kg of body weight may be administered intramuscularly or subcutaneously with each dose or with alternate doses of neostigmine to counteract the muscarinic side effects 19.

Antidote (to nondepolarizing neuromuscular block)¾Intravenous, 40 mcg (0.04 mg) per kg of body weight administered with 20 mcg (0.02 mg) of atropine per kg of body weight 32.

[Diagnostic aid (myasthenia gravis)] *¾Intramuscular, 40 mcg (0.04 mg) per kg of body weight or 1 mg per square meter of body surface per dose 26.

Intravenous, 20 mcg (0.02 mg) per kg of body weight or 500 mcg (0.5 mg) per square meter of body surface 26.

Usual geriatric dose

See Usual adult and adolescent dose .

Strength(s) usually available

U.S.¾0.25 mg per mL (1:4000) (Rx)[Prostigmin (parabens 0.2% [methyl and propyl]) (sodium hydroxide)] [Generic] 12

0.5 mg per mL (1:2000) (Rx)[Prostigmin 12 (parabens 0.2% [methyl and propyl]) (sodium hydroxide¾in 1-ml ampuls) (phenol 0.45%) (sodium acetate 0.02%) (acetic acid) (sodium hydroxide¾in 10-mL vials)] [Generic]

1 mg per mL (1:1000) (Rx)[Prostigmin 12 (phenol 0.45%) (sodium acetate 0.02%) (acetic acid) (sodium hydroxide)] [Generic]

Canada¾0.5 mg per mL (1:2000) (Rx)[Prostigmin 14 (methylparaben 1.8 mg) (propylparaben 0.2 mg) (sodium <0.01 mmol/mL¾in 1-mL ampuls) (phenol 0.45%) (sodium acetate) (acetic acid) (sodium <0.01 mmol/mL¾in 10-mL vials)]

1 mg per mL (1:1000) (Rx)[Prostigmin 14 (phenol 0.45%) (sodium acetate) (acetic acid) (sodium hydroxide) (sodium <0.01 mmol/mL))]

2.5 mg per mL (1:400) (Rx)[Prostigmin 14 (phenol 0.4%,) (sodium chloride) (sodium hydroxide) (sodium <0.01 mmol/mL)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing. Protect from light. 11, 14

PYRIDOSTIGMINE

Summary of Differences

Category¾ Parenteral pyridostigmine also indicated as an antidote (to nondepolarizing neuromuscular block).

Pharmacology/pharmacokinetics¾ Generally has shorter duration of action than ambenonium 19, 32 and a slower onset and longer duration of action than neostigmine 15, 16, 17, 19, 20, 32.

Precautions¾ Cross-sensitivity and/or related problems¾Contains bromide ion to which some patients may be sensitive.

Side/adverse effects¾ May produce a significantly lower degree and incidence of bradycardia, salivation, and gastrointestinal stimulation than neostigmine 17, 20.

Additional Dosing Information

See also General Dosing Information.

For oral dosage forms only:

· The syrup dosage form may be preferred for use in children and "brittle" myasthenic patients who require fractions of 60-mg doses. Also, the syrup is more easily swallowed, especially in the morning, by patients with bulbar involvement. 17

· It has been reported that the extended-release dosage form may pass intact through the gastrointestinal tract in patients with increased gastrointestinal activity or diarrhea. Use of other oral dosage forms may be required temporarily for continued control of symptoms.

Oral Dosage Forms

PYRIDOSTIGMINE BROMIDE SYRUP USP

Usual adult and adolescent dose

Antimyasthenic¾Initial¾Oral, 30 to 60 mg every three to four hours, the dosage being adjusted as required 37, 40, 41, 42, 43.

Maintenance¾Oral, 600 mg (range 60 mg to 1.5 grams) per day 17, 19, 20, 37.

Usual pediatric dose

Antimyasthenic¾ Oral, 7 mg per kg of body weight or 200 mg per square meter of body surface per day, divided into five or six doses 19, 20, 26.

Usual geriatric dose

See Usual adult and adolescent dose .

Strength(s) usually available

U.S.¾60 mg per 5 mL (Rx)[Mestinon (alcohol 5%) (glycerin) (lactic acid) (sodium benzoate) (sorbitol) (sucrose) (FD&C Red No. 40) (FD&C Blue No. 1) (flavors) (water)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing.

PYRIDOSTIGMINE BROMIDE TABLETS USP

Usual adult and adolescent dose

See Pyridostigmine Bromide Syrup USP .

Usual pediatric dose

See Pyridostigmine Bromide Syrup USP .

Usual geriatric dose

See Pyridostigmine Bromide Syrup USP .

Strength(s) usually available

U.S.¾60 mg (Rx)[Mestinon 17 (scored) (lactose) (silicon dioxide) (stearic acid)]

Canada¾60 mg (Rx)[Mestinon 15 (scored) (lactose 272 mg)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

PYRIDOSTIGMINE BROMIDE EXTENDED-RELEASE TABLETS

Usual adult and adolescent dose

Antimyasthenic¾ Oral, 180 to 540 mg one or two times a day [15], [17], with at least six hours between doses [17].

Note: For optimum control of symptoms, it may be necessary to administer the more rapidly acting regular tablet or syrup dosage form concurrently with extended-release therapy [17].

Extended-release preparations may increase the risk of cholinergic crisis and, therefore, are usually not recommended.

Usual pediatric dose

Dosage has not been established.

Usual geriatric dose

See Usual adult and adolescent dose.

Strength(s) usually available

U.S.¾180 mg (Rx)[Mestinon Timespans 17 (carnauba wax) (corn-derived proteins) (magnesium stearate) (silica gel) (tribasic calcium phosphate)]

Canada¾180 mg (Rx)[Mestinon-SR (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Swallow tablets whole [15].

Parenteral Dosage Forms

PYRIDOSTIGMINE BROMIDE INJECTION USP

Usual adult and adolescent dose

Antimyasthenic¾Intramuscular or intravenous, 2 mg (approximately one-thirtieth of the usual oral dose [16], [32]) every two to three hours [8], [19].

Antidote (to nondepolarizing neuromuscular block):¾Intravenous, 10 to 20 mg [8], [9], [16].

Note: Prior to administration of pyridostigmine, it is recommended that 600 mcg (0.6 mg) to 1.2 mg of atropine sulfate be given intravenously to counteract the muscarinic effects [8], [9], [16].

Usual pediatric dose

Antimyasthenic¾Neonates of myasthenic mothers¾Intramuscular, 50 to 150 mcg (0.05 to 0.15 mg) per kg of body weight 8, 16, 19, 37 every four to six hours.

Usual geriatric dose

See Usual adult and adolescent dose.

Strength(s) usually available

U.S.¾5 mg per mL (Rx)[Mestinon 16 (parabens 0.2% [methyl and propyl]) (sodium citrate 0.02%) (citric acid) (sodium hydroxide)] [Regonol 9 (benzyl alcohol 1%)]

Canada¾5 mg per mL (Rx)[Regonol 8 (parabens 0.2% [methyl and propyl]) (sodium citrate 0.02%) (citric acid) (sodium hydroxide)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. 9 Protect from freezing.