Descargar Fichas Tecnicas

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Calle 15 65-B # 221 X 128
Fracc Yucalpetén C.p 97238
Mérida Yuc.
Cel: 9999-109946

Medicina Interna

1. Pilocarpine

2. Potassium Citrate

3. Baclofen

4. Bethanechol

5. Sotalol

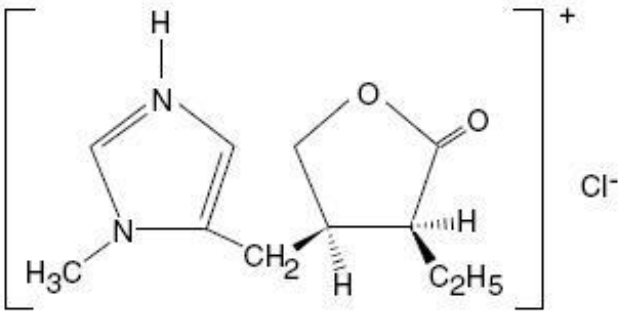
6. Fludrocortisone

PILOCARPINE HYDROCHLORIDE- pilocarpine hydrochloride tablet, film coated
Lannett Company, Inc.

Pilocarpine Hydrochloride Tablets, USP
Rx Only

DESCRIPTION:

Pilocarpine hydrochloride tablets, USP contain pilocarpine hydrochloride, a cholinergic agonist for oral use. Pilocarpine hydrochloride, USP is a hygroscopic, odorless, bitter tasting white crystal or powder which is soluble in water and alcohol and virtually insoluble in most non-polar solvents. Pilocarpine hydrochloride, USP with a chemical name of (3S-*cis*)-2(3*H*)-Furanone, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]monohydrochloride, has a molecular weight of 244.72.



Each 5 mg Pilocarpine Hydrochloride Tablet, USP for oral administration contains 5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet are microcrystalline cellulose and stearic acid, the tablet's film coating is: polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Each 7.5 mg Pilocarpine Hydrochloride Tablet, USP for oral administration contains 7.5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet are microcrystalline cellulose and stearic acid, the tablet's film coating is: FD&C Blue #2/Indigo Carmine aluminum lake, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

CLINICAL PHARMACOLOGY:

Pharmacodynamics:

Pilocarpine is a cholinergic parasympathomimetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action. Pilocarpine, in appropriate dosage, can increase secretion by the exocrine glands. The sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucous cells of the respiratory tract may be stimulated. When applied topically to the eye as a single dose it causes miosis, spasm of accommodation, and may cause a transitory rise in intraocular pressure followed by a more persistent fall. Dose-related smooth muscle stimulation of the intestinal tract may cause increased tone, increased motility, spasm, and tenesmus.

Bronchial smooth muscle tone may increase. The tone and motility of urinary tract, gallbladder, and biliary duct smooth muscle may be enhanced. Pilocarpine may have paradoxical effects on the cardiovascular system. The expected effect of a muscarinic agonist is vasodepression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

In a study of 12 healthy male volunteers there was a dose-related increase in unstimulated salivary flow following single 5 and 10 mg oral doses of pilocarpine hydrochloride tablets. This effect of pilocarpine on salivary flow was time-related with an onset at 20 minutes and a peak effect at 1 hour with a duration of 3 to 5 hours (See **Pharmacokinetics** section).

Head & Neck Cancer Patients:

In a 12 week randomized, double-blind, placebo-controlled study in 207 patients (placebo, N=65; 5 mg, N=73; 10 mg, N=69), increases from baseline (means 0.072 and 0.112 mL/min, ranges −0.690 to 0.728 and −0.380 to 1.689) of whole saliva flow for the 5 mg (63%) and 10 mg (90%) tablet, respectively, were seen 1 hour after the first dose of pilocarpine hydrochloride tablets. Increases in unstimulated parotid flow were seen following the first dose (means 0.025 and 0.046 mL/min, ranges 0 to 0.414 and −0.070 to 1.002 mL/min for the 5 and 10 mg dose, respectively). In this study, no correlation existed between the amount of increase in salivary flow and the degree of symptomatic relief.

Sjogren's Syndrome Patients:

In two 12 week randomized, double-blind, placebo-controlled studies in 629 patients (placebo, n=253; 2.5 mg, n=121; 5 mg, n=255; 5-7.5 mg, n=114), the ability of pilocarpine hydrochloride tablets to stimulate saliva production was assessed. In these trials using varying doses of pilocarpine hydrochloride tablets (2.5-7.5 mg), the rate of saliva production was plotted against time. An Area Under the Curve (AUC) representing the total amount of saliva produced during the observation interval was calculated. Relative to placebo, an increase in the amount of saliva being produced was observed following the first dose of pilocarpine hydrochloride tablets and was maintained throughout the duration (12 weeks) of the trials in an approximate dose response fashion (See **Clinical Studies** section).

Pharmacokinetics:

In a multiple-dose pharmacokinetic study in male volunteers following 2 days of 5 or 10 mg of oral pilocarpine hydrochloride tablets given at 8 a.m., noontime, and 6 p.m., the mean elimination half-life was 0.76 hours for the 5 mg dose and 1.35 hours for the 10 mg dose. T_{max} values were 1.25 hours and 0.85 hours. C_{max} values were 15 ng/mL and 41 ng/mL. The AUC trapezoidal values were 33 h(ng/mL) and 108 h(ng/mL), respectively, for the 5 and 10 mg doses following the last 6 hour dose.

Pharmacokinetics in elderly male volunteers (n = 11) were comparable to those in younger men. In five healthy elderly female volunteers, the mean C_{max} and AUC were approximately twice that of elderly males and young normal male volunteers.

When taken with a high fat meal by 12 healthy male volunteers, there was a decrease in the rate of absorption of pilocarpine from pilocarpine hydrochloride tablets. Mean $T_{max's}$

were 1.47 and 0.87 hours, and mean $C_{max's}$ were 51.8 and 59.2 ng/mL for fed and fasted, respectively.

Limited information is available about the metabolism and elimination of pilocarpine in humans. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. Pilocarpine and its minimally active or inactive degradation products, including pilocarpic acid, are excreted in the urine. Pilocarpine does not bind to human or rat plasma proteins over a concentration range of 5 to 25,000 ng/mL. The effect of pilocarpine on plasma protein binding of other drugs has not been evaluated.

In patients with mild to moderate hepatic impairment (n=12), administration of a single 5 mg dose resulted in a 30% decrease in total plasma clearance and a doubling of exposure (as measured by AUC). Peak plasma levels were also increased by about 30% and half-life was increased to 2.1 hrs.

There were no significant differences in the pharmacokinetics of oral pilocarpine in volunteer subjects (n=8) with renal insufficiency (mean creatinine clearances 25.4 mL/min; range 9.8 – 40.8 mL/min) compared to the pharmacokinetics previously observed in normal volunteers.

Clinical Studies:

Head & Neck Cancer Patients:

A 12 week randomized, double-blind, placebo-controlled study in 207 patients (142 men, 65 women) was conducted in patients whose mean age was 58.5 years with a range of 19 to 77; the racial distribution was Caucasian 95%, Black 4%, and other 1%. In this population, a statistically significant improvement in mouth dryness occurred in the 5 and 10 mg pilocarpine hydrochloride tablet treated patients compared to placebo treated patients. The 5 and 10 mg treated patients could not be distinguished. (See **Pharmacodynamics** section for flow study details.)

Another 12 week, double-blind, randomized, placebo-controlled study was conducted in 162 patients whose mean age was 57.8 years with a range of 27 to 80; the racial distribution was Caucasian 88%, Black 10%, and other 2%. The effects of placebo were compared to 2.5 mg three times a day of pilocarpine hydrochloride tablets for 4 weeks followed by adjustment to 5 mg three times a day and 10 mg three times a day. Lowering of the dose was necessary because of adverse events in 3 of 67 patients treated with 5 mg of pilocarpine hydrochloride tablets and in 7 of 66 patients treated with 10 mg of pilocarpine hydrochloride tablets. After 4 weeks of treatment, 2.5 mg of pilocarpine hydrochloride tablets three times a day was comparable to placebo in relieving dryness. In patients treated with 5 mg and 10 mg of pilocarpine hydrochloride tablets, the greatest improvement in dryness was noted in patients with no measurable salivary flow at baseline.

In both studies, some patients noted improvement in the global assessment of their dry mouth, speaking without liquids, and a reduced need for supplemental oral comfort agents.

In the two placebo-controlled clinical trials, the most common adverse events related to drug, and increasing in rate as dose increases, were sweating, nausea, rhinitis, diarrhea, chills, flushing, urinary frequency, dizziness, and asthenia. The most common adverse experience causing withdrawal from treatment was sweating (5 mg t.i.d. ≤1%; 10 mg

t.i.d. =12%).

Sjogren's Syndrome Patients:

Two separate studies were conducted in patients with primary or secondary Sjogren's Syndrome. In both studies, the majority of patients best fit the European criteria for having primary Sjogren's Syndrome. ["Criteria for the Classification of Sjogren's Syndrome" (Vitali C, Bombardieri S, Moutsopoulos HM, et al: Preliminary criteria for the classification of Sjogren's syndrome. Arthritis Rheum 36:340-347, 1993.)]

A 12-week, randomized, double-blind, parallel-group, placebo-controlled study was conducted in 256 patients (14 men, 242 women) whose mean age was 57 years with a range of 24 to 85 years. The racial distribution was as follows: Caucasian 91%, Black 6%, and other 3%.

The effects of placebo were compared with those of pilocarpine hydrochloride tablets 5 mg four times a day (20 mg/day) for 6 weeks. At 6 weeks, the patients' dosage was increased from 5 mg pilocarpine hydrochloride tablets q.i.d. to 7.5 mg q.i.d. The data collected during the first 6 weeks of the trial were evaluated for safety and efficacy, and the data of the second 6 weeks of the trial were used to provide additional evidence of safety.

After 6 weeks of treatment, statistically significant global improvement of dry mouth was observed compared to placebo. "Global improvement" is defined as a score of 55 mm or more on a 100 mm visual analogue scale in response to the question, "Please rate your present condition of dry mouth (xerostomia) compared with your condition at the start of this study. Consider the changes to your dry mouth and other symptoms related to your dry mouth that have occurred since you have taken this medication." Patients' assessments of specific dry mouth symptoms such as severity of dry mouth, mouth discomfort, ability to speak without water, ability to sleep without drinking water, ability to swallow food without drinking, and a decreased use of saliva substitutes were found to be consistent with the significant global improvement described.

Another 12 week randomized, double-blind, parallel-group, placebo-controlled study was conducted in 373 patients (16 men, 357 women) whose mean age was 55 years with a range of 21 to 84. The racial distribution was Caucasian 80%, Oriental 14%, Black 2%, and 4% of other origin. The treatment groups were 2.5 mg pilocarpine tablets, 5 mg pilocarpine hydrochloride tablets, and placebo. All treatments were administered on a four times a day regimen.

After 12 weeks of treatment, statistically significant global improvement of dry mouth was observed at a dose of 5 mg compared with placebo. The 2.5 mg (10mg/day) group was not significantly different than placebo. However, a subgroup of patients with rheumatoid arthritis tended to improve in global assessments at both the 2.5 mg q.i.d. (9 patients) and 5 mg q.i.d. (16 patients) dose (10-20 mg/day). The clinical significance of this finding is unknown.

Patients' assessments of specific dry mouth symptoms such as severity of dry mouth, mouth discomfort, ability to sleep without drinking water, and decreased use of saliva substitutes were also found to be consistent with the significant global improvement described when measured after 6 weeks and 12 weeks of pilocarpine hydrochloride tablets use.

INDICATIONS AND USAGE:

Pilocarpine hydrochloride tablets, USP are indicated for 1) the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck; and 2) the treatment of symptoms of dry mouth in patients with Sjogren's syndrome.

CONTRAINDICATIONS:

Pilocarpine hydrochloride tablets are contraindicated in patients with uncontrolled asthma, known hypersensitivity to pilocarpine, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle closure) glaucoma.

WARNINGS:

Cardiovascular Disease:

Patients with significant cardiovascular disease may be unable to compensate for transient changes in hemodynamics or rhythm induced by pilocarpine. Pulmonary edema has been reported as a complication of pilocarpine toxicity from high ocular doses given for acute angle-closure glaucoma. Pilocarpine should be administered with caution in and under close medical supervision of patients with significant cardiovascular disease.

Ocular:

Ocular formulations of pilocarpine have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

Pulmonary Disease:

Pilocarpine has been reported to increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Pilocarpine hydrochloride should be administered with caution to and under close medical supervision in patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease requiring pharmacotherapy.

PRECAUTIONS:

General:

Pilocarpine toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

The dose-related cardiovascular pharmacologic effects of pilocarpine include hypotension, hypertension, bradycardia, and tachycardia.

Pilocarpine should be administered with caution to patients with known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis, and biliary obstruction.

Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic (or "ureteral reflux"), particularly in patients with nephrolithiasis.

Cholinergic agonists may have dose-related central nervous system effects. This should be considered when treating patients with underlying cognitive or psychiatric disturbances.

Hepatic Insufficiency:

Based on decreased plasma clearance observed in patients with moderate hepatic impairment, the starting dose in these patients should be 5 mg twice daily, followed by adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency (Child-Pugh score of 5-6) do not require dosage reductions. To date, pharmacokinetic studies in subjects with severe hepatic impairment (Child-Pugh score of 10-15) have not been carried out. The use of pilocarpine in these patients is not recommended.

Child-Pugh scoring system for Hepatic Impairment

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg. per 100 ml.)	1-2	2-3	>3
Albumin (g. per 100 ml.)	3-5	2.8-3.5	<2.8
Prothrombin time (sec. Prolonged)	1-4	4-6	>6
For primary biliary cirrhosis:- Bilirubin (mg. per 100 ml.)	1-4	4-10	>10

* According to grading of Trey, Burns, and Saunders (1966)

Reference: Pugh, R.N.H., Murray-Lyon, I.M., Dawson, J.L. Pietroni, M.C., Williams, R. 1973, Transection of the Oesophagus for Bleeding Oesophageal Varices, *Brit. J. Surg.*, 60:646-9.

Information for Patients:

Patients should be informed that pilocarpine may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking pilocarpine hydrochloride and cannot drink enough liquid, the patient should consult a physician. Dehydration may develop.

Drug Interactions:

Pilocarpine should be administered with caution to patients taking beta adrenergic

antagonists because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with pilocarpine would be expected to result in additive pharmacologic effects.

Pilocarpine might antagonize the anticholinergic effects of drugs used concomitantly. These effects should be considered when anticholinergic properties may be contributing to the therapeutic effect of concomitant medication (e.g., atropine, inhaled ipratropium).

While no formal drug interaction studies have been performed, the following concomitant drugs were used in at least 10% of patients in either or both Sjogren's efficacy studies: acetylsalicylic acid, artificial tears, calcium, conjugated estrogens, hydroxychloroquine sulfate, ibuprofen, levothyroxine sodium, medroxyprogesterone acetate, methotrexate, multivitamins, naproxen, omeprazole, paracetamol, and prednisone.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage studied (up to 30 mg/kg/day, which yielded a systemic exposure approximately 50 times larger than the maximum systemic exposure observed clinically). In rats, a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both males and females, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats. The tumorigenicity observed in rats was observed only at a large multiple of the maximum labeled clinical dose, and may not be relevant to clinical use.

No evidence that pilocarpine has the potential to cause genetic toxicity was obtained in a series of studies that included: 1) bacterial assays (*Salmonella* and *E. coli*) for reverse gene mutations; 2) an *in vitro* chromosome aberration assay in a Chinese hamster ovary cell line; 3) an *in vivo* chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Oral administration of pilocarpine to male and female rats at a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on male animals, female animals, or both males and females. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day (approximately 3 times the maximum recommended human dose when compared on the basis of body surface area (mg/m^2) estimates) for six months resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair the fertility of male and female humans. Pilocarpine hydrochloride tablets should be administered to individuals who are attempting to conceive a child only if the potential benefit justifies potential impairment of fertility.

Pregnancy:

Teratogenic effects

Pregnancy Category C:

Pilocarpine was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 mg/kg/day (approximately 26 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates). These effects may have been secondary to maternal toxicity. In another study, oral administration of pilocarpine to female rats during gestation and lactation at a dosage of 36 mg/kg/day (approximately 10 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates) resulted in an increased incidence of stillbirths; decreased neonatal survival and reduced mean body weight of pups were observed at dosages of 18 mg/kg/day (approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates) and above. There are no adequate and well-controlled studies in pregnant women. Pilocarpine hydrochloride tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pilocarpine hydrochloride tablets, 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.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Head and Neck Cancer Patients:

In the placebo-controlled clinical trials (see **Clinical Studies** section) the mean age of patients was approximately 58 years (range 19 to 80). Of these patients, 97/369 (61/217 receiving pilocarpine) were over the age of 65 years. In the healthy volunteer studies, 15/150 subjects were over the age of 65 years. In both study populations, the adverse events reported by those over 65 years and those 65 years and younger were comparable. Of the 15 elderly volunteers (5 women, 10 men), the 5 women had higher $C_{max's}$ and AUC's than the men. (See **Pharmacokinetics** section.)

Sjogren's Syndrome Patients:

In the placebo-controlled clinical trials (see **Clinical Studies** section), the mean age of patients was approximately 55 years (range 21 to 85). The adverse events reported by those over 65 years and those 65 years and younger were comparable except for notable trends for urinary frequency, diarrhea, and dizziness (see **ADVERSE REACTIONS** section).

ADVERSE REACTIONS:

Head & Neck Cancer Patients:

In controlled studies, 217 patients received pilocarpine, of whom 68% were men and 32% were women. Race distribution was 91% Caucasian, 8% Black, and 1% of other origin. Mean age was approximately 58 years. The majority of patients were between 50 and 64 years (51%), 33% were 65 years and older and 16% were younger than 50 years of age.

The most frequent adverse experiences associated with pilocarpine hydrochloride tablets were a consequence of the expected pharmacologic effects of pilocarpine.

Adverse Event	**Pilocarpine HCl**		**Placebo**
	10 mg t.i.d. (30 mg/day)	5 mg t.i.d. (15 mg/day)	(t.i.d.)
	n=121	n=141	n=152
Sweating	68%	29%	9%
Nausea	15	6	4
Rhinitis	14	5	7
Diarrhea	7	4	5
Chills	15	3	<1
Flushing	13	8	3
Urinary Frequency	12	9	7
Dizziness	12	5	4
Asthenia	12	6	3

In addition, the following adverse events (≥3% incidence) were reported at dosages of 15-30 mg/day in the controlled clinical trials:

Adverse Event	**Pilocarpine HCl**	**Placebo**
	5-10 mg t.i.d. (15-30 mg/day)	(t.i.d.)
	n=212	n=152
Headache	11%	8%
Dyspepsia	7	5
Lacrimation	6	8
Edema	5	4
Abdominal Pain	4	4
Amblyopia	4	2
Vomiting	4	1
Pharyngitis	3	8
Hypertension	3	1

The following events were reported with treated head and neck cancer patients at incidences of 1% to 2% at dosages of 7.5 to 30 mg/day: abnormal vision, conjunctivitis, dysphagia, epistaxis, myalgias, pruritus, rash, sinusitis, tachycardia, taste perversion, tremor, voice alteration.

The following events were reported rarely in treated head and neck cancer patients

(<1%): Causal relation is unknown.

Body as a whole: body odor, hypothermia, mucous membrane abnormality

Cardiovascular: bradycardia, ECG abnormality, palpitations, syncope

Digestive: anorexia, increased appetite, esophagitis, gastrointestinal disorder, tongue disorder

Hematologic: leukopenia, lymphadenopathy

Nervous: anxiety, confusion, depression, abnormal dreams, hyperkinesia, hypesthesia, nervousness, paresthesias, speech disorder, twitching

Respiratory: increased sputum, stridor, yawning

Skin: seborrhea

Special senses: deafness, eye pain, glaucoma

Urogenital: dysuria, metrorrhagia, urinary impairment

In long-term treatment were two patients with underlying cardiovascular disease of whom one experienced a myocardial infarct and another episode of syncope. The association with drug is uncertain.

Sjogren's Syndrome Patients:

In controlled studies, 376 patients received pilocarpine, of whom 5% were men and 95% were women. Race distribution was 84% Caucasian, 9% Oriental, 3% Black, and 4% of other origin. Mean age was 55 years. The majority of patients were between 40 and 69 years (70%), 16% were 70 years and older and 14% were younger than 40 years of age. Of these patients, 161/629 (89/376 receiving pilocarpine) were over the age of 65 years. The adverse events reported by those over 65 years and those 65 years and younger were comparable except for notable trends for urinary frequency, diarrhea, and dizziness. The incidences of urinary frequency and diarrhea in the elderly were about double those in the non-elderly. The incidence of dizziness was about three times as high in the elderly as in the non-elderly. These adverse experiences were not considered to be serious. In the 2 placebo-controlled studies, the most common adverse events related to drug use were sweating, urinary frequency, chills, and vasodilatation (flushing). The most commonly reported reason for patient discontinuation of treatment was sweating. Expected pharmacologic effects of pilocarpine include the following adverse experiences associated with pilocarpine hydrochloride tablets:

Adverse Event	**Pilocarpine HCl** 5 mg q.i.d. (20 mg/day) n=255	**Placebo** (q.i.d.) n=253
Sweating	40%	7%
Urinary Frequency	10	4
Nausea	9	9
Flushing	9	2
Rhinitis	7	8

Diarrhea	6	7
Chills	4	2
Increased Salivation	3	0
Asthenia	2	2

In addition, the following adverse events (≥3% incidence) were reported at dosages of 15-30 mg/day in the controlled clinical trials:

Adverse Event	**Pilocarpine HCl** 5 mg q.i.d. (20 mg/day) n=255	**Placebo** (q.i.d.) n=253
Headache	13%	19%
Flu Syndrome	9	9
Dyspepsia	7	7
Dizziness	6	7
Pain	4	2
Sinusitis	4	5
Abdominal Pain	3	4
Vomiting	3	1
Pharyngitis	2	5
Rash	2	3
Infection	2	6

The following events were reported with treated head and neck cancer patients at incidences of 1% to 2% at dosages of 7.5 to 30 mg/day: abnormal vision, conjunctivitis, dysphagia, epistaxis, myalgias, pruritus, rash, sinusitis, tachycardia, taste perversion, tremor, voice alteration.

The following events were reported rarely in treated Sjogren's patients (<1%) at dosing of 10-30 mg/day: Causal relation is unknown.

Body as a whole: chest pain, cyst, death, moniliasis, neck pain, neck rigidity, photosensitivity reaction

Cardiovascular: angina pectoris, arrhythmia, ECG abnormality, hypotension, hypertension, intracranial hemorrhage, migraine, myocardial infarction

Digestive: anorexia, bilirubinemia, cholelithiasis, colitis, dry mouth, eructation, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, hepatitis, abnormal liver function tests, melena, nausea & vomiting, pancreatitis, parotid gland enlargement, salivary gland enlargement, sputum increased, taste loss, tongue disorder, tooth disorder

Hematologic: hematuria, lymphadenopathy, abnormal platelets, thrombocythemia, thrombocytopenia, thrombosis, abnormal WBC

Metabolic and Nutritional: peripheral edema, hypoglycemia

Musculoskeletal: arthralgia, arthritis, bone disorder, spontaneous bone fracture, pathological fracture, myasthenia, tendon disorder, tenosynovitis

Nervous: aphasia, confusion, depression, abnormal dreams, emotional lability, hyperkinesia, hypesthesia, insomnia, leg cramps, nervousness, paresthesias, abnormal thinking, tremor

Respiratory: bronchitis, dyspnea, hiccup, laryngismus, laryngitis, pneumonia, viral infection, voice alteration

Skin: alopecia, contact dermatitis, dry skin, eczema, erythema nodosum, exfoliative dermatitis, herpes simplex, skin ulcer, vesiculobullous rash

Special senses: cataract, conjunctivitis, dry eyes, ear disorder, ear pain, eye disorder, eye hemorrhage, glaucoma, lacrimation disorder, retinal disorder, taste perversion, abnormal vision

Urogenital: breast pain, dysuria, mastitis, menorrhagia, metrorrhagia, ovarian disorder, pyuria, salpingitis, urethral pain, urinary urgency, vaginal hemorrhage, vaginal moniliasis

The following adverse experiences have been reported rarely with ocular pilocarpine: A-V block, agitation, ciliary congestion, confusion, delusion, depression, dermatitis, middle ear disturbance, eyelid twitching, malignant glaucoma, iris cysts, macular hole, shock, and visual hallucination.

MANAGEMENT OF OVERDOSE:

Fatal overdosage with pilocarpine has been reported in the scientific literature at doses presumed to be greater than 100 mg in two hospitalized patients. 100 mg of pilocarpine is considered potentially fatal. Overdosage should be treated with atropine titration (0.5 mg to 1.0 mg given subcutaneously or intravenously) and supportive measures to maintain respiration and circulation. Epinephrine (0.3 mg to 1.0 mg, subcutaneously or intramuscularly) may also be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if pilocarpine is dialyzable.

DOSAGE AND ADMINISTRATION:

Regardless of the indication, the starting dose in patients with moderate hepatic impairment should be 5 mg twice daily, followed by adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency do not require dosage reductions. The use of pilocarpine in patients with severe hepatic insufficiency is not recommended. If needed, refer to the *Hepatic Insufficiency* subsection of the **Precautions** section of this label for definitions of mild, moderate and severe hepatic impairment.

Head & Neck Cancer Patients:

The recommended initial dose of pilocarpine hydrochloride tablets is 5 mg taken three times a day. Dosage should be titrated according to therapeutic response and tolerability. The usual dosage range is 15-30 mg per day. (Not to exceed 10 mg per dose.) Although early improvement may be realized, at least 12 weeks of uninterrupted therapy with pilocarpine hydrochloride tablets may be necessary to assess whether a beneficial response will be achieved. The incidence of the most common adverse events increases with dose. The lowest dose that is tolerated and effective should be used for maintenance.

Sjogren's Syndrome Patients:

The recommended dose of pilocarpine hydrochloride tablets is one tablet (5 mg) taken four times a day. Efficacy was established by 6 weeks of use.

HOW SUPPLIED:

Pilocarpine hydrochloride tablets USP, 5 mg are white, film coated, round tablets, debossed LAN on one side and 1313 on the other side. Each tablet contains 5 mg pilocarpine hydrochloride. They are supplied as follows:

NDC 0527-1313-01 bottles of 100

Store at 20°- 25°C (68°-77°F) [see USP Controlled Room Temperature].

Pilocarpine hydrochloride tablets USP, 7.5 mg are blue, film coated, round tablets, debossed LCI on one side and 1407 on the other side. Each tablet contains 7.5 mg pilocarpine hydrochloride. They are supplied as follows:

NDC 0527-1407-01 bottles of 100

Store at 20°- 25°C (68°-77°F) [see USP Controlled Room Temperature].

Distributed by:
Lannett Company, Inc.
Philadelphia, PA 19136

CIB70322D

Rev. 10/24

PRINCIPAL DISPLAY PANEL — 5 mg

NDC 0527-**1313-**01

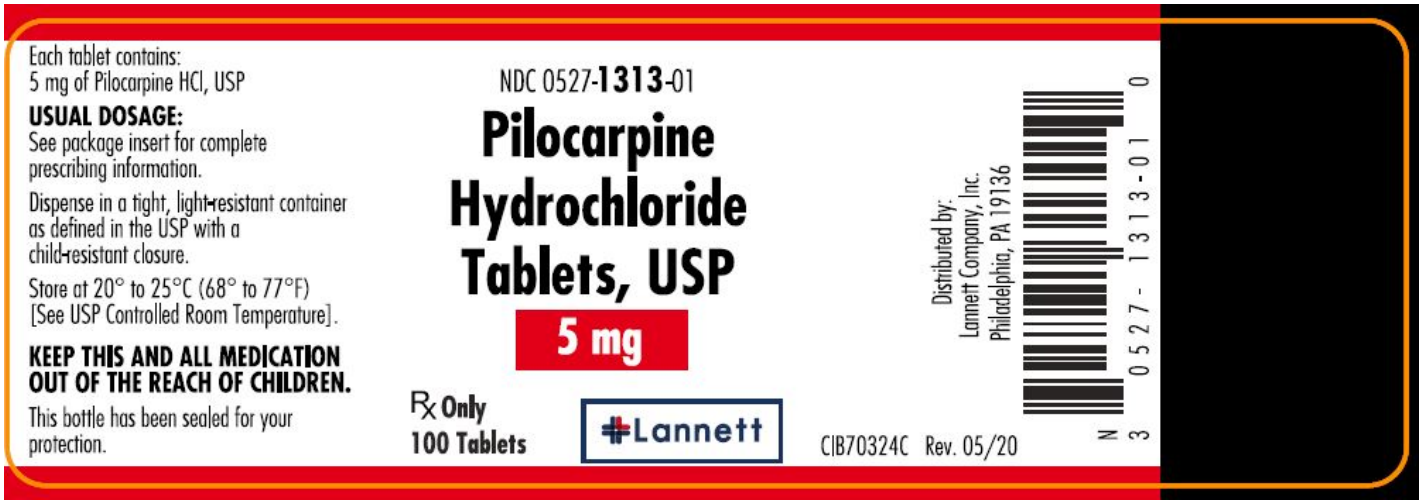
Pilocarpine
Hydrochloride
Tablets, USP

5 mg

Rx Only

100 Tablets

Lannett



PRINCIPAL DISPLAY PANEL — 7.5 mg

NDC 0527-**1407**-01

Pilocarpine Hydrochloride Tablets, USP

7.5 mg

Rx Only

100 Tablets

Lannett

PILOCARPINE HYDROCHLORIDE

pilocarpine hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0527-1313

Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PILOCARPINE HYDROCHLORIDE (UNII: 0WW6D218XJ) (PILOCARPINE - UNII:01MI4Q9DI3)	PILOCARPINE HYDROCHLORIDE	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	LAN;1313
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0527-1313-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/14/2005	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077220	10/14/2005	

PILOCARPINE HYDROCHLORIDE

pilocarpine hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0527-1407
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PILOCARPINE HYDROCHLORIDE (UNII: 0WW6D218XJ) (PILOCARPINE - UNII:01MI4Q9DI3)	PILOCARPINE HYDROCHLORIDE	7.5 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
INDIGOTINDISULFONATE SODIUM (UNII: D3741U8K7L)	
ALUMINUM OXIDE (UNII: LMI26O6933)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	blue	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	LCI;1407
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0527-1407-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/14/2005	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077220	10/14/2005	

Labeler - Lannett Company, Inc. (002277481)

Establishment

Name	Address	ID/FEI	Business Operations
Lannett Company, Inc.		006422406	analysis(0527-1313, 0527-1407) , label(0527-1313, 0527-1407) , manufacture(0527-1313, 0527-1407) , pack(0527-1313, 0527-1407)

Revised: 10/2024 Lannett Company, Inc.

POTASSIUM CITRATE AND CITRIC ACID- potassium citrate and citric acid monohydrate solution
Pharmaceutical Associates, Inc.

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

Potassium Citrate and Citric Acid Oral Solution USP

Rx ONLY

DESCRIPTION

Potassium Citrate and Citric Acid Oral Solution USP is a stable and pleasant-tasting oral systemic alkalizer containing potassium citrate and citric acid in a sugar-free, non-alcoholic base.

Potassium Citrate and Citric Acid Oral Solution USP contains in each teaspoonful (5 mL):

POTASSIUM CITRATE Monohydrate 1100 mg

CITRIC ACID Monohydrate 334 mg

Each mL contains 2 mEq potassium ion and is equivalent to 2 mEq bicarbonate (HCO_3).

Inactive Ingredients: FD&C Red No. 40, flavoring, polyethylene glycol, propylene glycol, purified water, sodium benzoate, and sorbitol solution.

ACTIONS

Potassium citrate is absorbed and metabolized to potassium bicarbonate, thus acting as a systemic alkalizer. The effects are essentially those of chlorides before absorption and those of bicarbonates subsequently. Oxidation is virtually complete so that less than 5% of the potassium citrate is excreted in the urine unchanged.

INDICATIONS AND USAGE

Potassium Citrate and Citric Acid Oral Solution USP is an effective alkalinizing agent useful in those conditions where long-term maintenance of an alkaline urine is desirable, such as in patients with uric acid and cystine calculi of the urinary tract, especially when the administration of sodium salts is undesirable or contraindicated. In addition, it is a valuable adjuvant when administered with uricosuric agents in gout therapy, since urates tend to crystallize out of an acid urine. It is also effective in correcting the acidosis of certain renal tubular disorders where the administration of potassium citrate may be preferable. This product is highly concentrated, and when administered after meals and before bedtime, allows one to maintain an alkaline urinary pH around the clock, usually without the necessity of a 2 A.M. dose. This product alkalinizes the urine without producing a systemic alkalosis in recommended dosage. It is highly palatable, pleasant tasting and tolerable, even when administered for long periods. Potassium citrate does not neutralize the gastric juice or disturb digestion.

CONTRAINDICATIONS

Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, anuria, severe myocardial damage, and hyperkalemia from any cause.

WARNINGS

Large doses may cause hyperkalemia and alkalosis, especially in the presence of renal disease. Concurrent administration of potassium-containing medication, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, or cardiac glycosides may lead to toxicity.

PRECAUTIONS

Should be used with caution by patients with low urinary output unless under the supervision of a physician. As with all liquids containing a high concentration of potassium, patients should be directed to dilute adequately with water to minimize the possibility of gastrointestinal injury associated with the oral ingestion of concentrated potassium salt preparations; and preferably, to take each dose after meals to avoid saline laxative effect.

ADVERSE REACTIONS

Potassium Citrate and Citric Acid Oral Solution USP is generally well tolerated without any unpleasant side effects when given in recommended doses to patients with normal renal function and urinary output. However, as with any alkalinizing agent, caution must be used in certain patients with abnormal renal mechanisms to avoid development of hyperkalemia or alkalosis. Potassium intoxication causes listlessness, weakness, mental confusion, tingling of extremities, and other symptoms associated with a high concentration of potassium in the serum. Periodic determinations of serum electrolytes should be carried out in those patients with renal disease in order to avoid these complications. Hyperkalemia may exhibit the following electrocardiographic abnormalities: Disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired, hyperkalemia can result (see Contraindications and Warnings). Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA

Should hyperkalemia occur, treatment measures include the following: (1) Elimination of

foods or medications containing potassium. (2) The intravenous administration of 300 to 500 mL/hr of dextrose solution (10 to 25%), containing 10 units of insulin/20 gm dextrose. (3) The use of exchange resins, hemodialysis, or peritoneal dialysis. In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the plasma potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION

Potassium Citrate and Citric Acid Oral Solution USP should be taken diluted in water according to directions, followed by additional water, if desired. Palatability is enhanced if chilled before taking.

Usual Adult Dose

3 to 6 teaspoonfuls (15 to 30 mL), diluted with 1 glass of water, after meals and at bedtime, or as directed by a physician.

Usual Pediatric Dose

1 to 3 teaspoonfuls (5 to 15 mL), diluted with 1/2 glass of water, after meals and at bedtime, or as directed by a physician.

Usual Dosage Range

2 to 3 teaspoonfuls (10 to 15 mL), diluted with a glassful of water, taken four times a day. Potassium Citrate and Citric Acid Oral Solution USP, diluted with a glassful of water, taken four times a day will usually maintain a urinary pH of 7.0-7.6 throughout most of the 24 hours without unpleasant side effects. To check urinary pH, HYDRION Paper (pH 6.0-8.0) or NITRAZINE Paper (pH 4.5-7.5) are available and easy to use.

HOW SUPPLIED

Potassium Citrate and Citric Acid Oral Solution USP (clear pink to red colored; berry-citrus flavored) is supplied in the following oral dosage form:

NDC 0121-0676-16: 16 fl oz (473 mL) bottle

STORAGE

Keep tightly closed. Store at controlled room temperature, 20°-25°C (68°-77°F). Protect from excessive heat and freezing.

MANUFACTURED BY

Pharmaceutical Associates, Inc. Greenville, SC 29605
www.paipharma.com

R03/17

PRINCIPAL DISPLAY PANEL - 473 mL Bottle Label

NDC 0121-0676-16

Potassium Citrate
and Citric Acid
Oral Solution USP
1100 mg/334 mg per 5 mL

A SUGAR-FREE SYSTEMIC ALKALIZER

Each teaspoonful (5 mL) contains:
Potassium Citrate Monohydrate.....1100 mg
Citric Acid Monohydrate.....334 mg

Each mL contains 2 mEq Potassium Ion, and is equivalent to 2 mEq Bicarbonate (HCO_3).

Rx ONLY

16 fl oz (473 mL)

Pharmaceutical
Associates, Inc.
Greenville, SC 29605

INDICATIONS AND USAGE: Potassium Citrate and Citric Acid Oral Solution USP is a stable and pleasant-tasting oral systemic alkalizer. It is effective for long-term maintenance of an alkaline urine, especially when the administration of sodium salts is undesirable or contra-indicated.

SEE ACCOMPANYING LITERATURE

DOSAGE AND ADMINISTRATION:

Usual Adult Dosage: 3 to 6 teaspoonfuls (15 to 30 mL) **DILUTED** with 1 glass of water, after meals and at bedtime, or as directed by a physician.

SHAKE WELL BEFORE USING.

STORAGE: Keep tightly closed. Store at controlled room temperature. 20° -25° C (68° -77° F). Protect from excessive heat or freezing.

Dispense in a tight, light-resistance container with a child-resistant closure.

L06761600
R08/14

POTASSIUM CITRATE AND CITRIC ACID

potassium citrate and citric acid monohydrate solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0121-0676
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
POTASSIUM CITRATE (UNII: EE90ONI6FF) (ANHYDROUS CITRIC ACID - UNII:XF417D3PSL)	POTASSIUM CITRATE	1100 mg in 5 mL
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP) (ANHYDROUS CITRIC ACID - UNII:XF417D3PSL)	ANHYDROUS CITRIC ACID	334 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
SORBITOL (UNII: 506T60A25R)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics			
Color	red	**Score**	
Shape		**Size**	
Flavor	BERRY	**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0121-0676-16	473 mL in 1 BOTTLE; Type 0: Not a Combination Product	10/07/1997	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		10/07/1997	

Labeler - Pharmaceutical Associates, Inc. (044940096)

Establishment

Name	Address	ID/FEI	Business Operations
Pharmaceutical Associates, Inc.		097630693	manufacture(0121-0676)

Revised: 1/2022 Pharmaceutical Associates, Inc.

BACLOFEN- baclofen tablet
Par Health USA, LLC

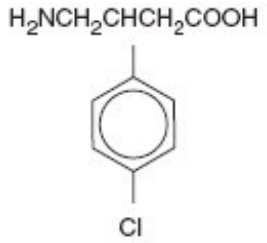
BACLOFEN TABLETS, USP

Rx only

DESCRIPTION

Baclofen, USP is a muscle relaxant and antispastic.

Its chemical name is 4-amino-3-(4-chlorophenyl)-butanoic acid. The structural formula is:



$C_{10}H_{12}ClNO_2$ M.W. = 213.66

Baclofen, USP is a white to creamy white powder. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

Baclofen Tablets USP 10 mg and 20 mg contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen is not fully known. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression. Baclofen is rapidly and extensively absorbed and eliminated. Absorption may be dose-dependent, being reduced with increasing doses. Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large intersubject variation in absorption and/or elimination.

INDICATIONS AND USAGE

Baclofen tablets USP are useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

Patients should have reversible spasticity so that baclofen treatment will aid in restoring residual function. Baclofen tablets USP may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

Baclofen tablets USP are not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.

The efficacy of baclofen in stroke, cerebral palsy, and Parkinson's disease has not been established and, therefore, it is not recommended for these conditions.

CONTRAINDICATIONS

Hypersensitivity to baclofen.

WARNINGS

1. Neonatal Withdrawal Symptoms: Withdrawal symptoms have been reported starting hours to days after delivery in neonates whose mothers were treated with oral baclofen throughout pregnancy. The symptoms of withdrawal in these infants have included increased muscle tone, tremor, jitteriness, and seizure. If the potential benefit justifies the potential risk to the fetus and oral baclofen is continued during pregnancy, gradually reduce the dose and discontinue baclofen before delivery. If slow withdrawal is not feasible, advise the parents or caregivers of the potential for neonatal withdrawal.
2. Abrupt Drug Withdrawal: Hallucinations and seizures have occurred on abrupt withdrawal of baclofen. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued.
3. Impaired Renal Function: Because baclofen is primarily excreted unchanged through the kidneys, it should be given with caution, and it may be necessary to reduce the dosage.
4. Stroke: Baclofen has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug.
5. Pregnancy: Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times the maximum dose recommended for human use, at a dose which caused significant reductions in food intake and weight gain in dams. This abnormality was not seen in mice or rabbits.

There was also an increased incidence of incomplete sternebral ossification in fetuses of rats given approximately 13 times the maximum recommended human dose, and an increased incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in fetuses of rabbits given approximately 7 times the maximum recommended human dose. In mice, no teratogenic effects were observed, although reductions in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 and 34 times the human daily dose. There are no studies in pregnant women. Baclofen should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of baclofen may be additive to those of alcohol and other CNS depressants.

Baclofen should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

In patients with epilepsy, the clinical state and electroencephalogram should be monitored at regular intervals, since deterioration in seizure control and EEG have been reported occasionally in patients taking baclofen.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

A dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands was observed in female rats treated chronically with baclofen.

Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients that were treated with baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

The most common is transient drowsiness (10 to 63%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen compared to 36% of those in the placebo group. Other common adverse reactions are dizziness (5 to 15%), weakness (5 to 15%) and fatigue (2 to 4%).

Others reported:

Neuropsychiatric: Confusion (1 to 11%), headache (4 to 8%), insomnia (2 to 7%); and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizure.

Cardiovascular: Hypotension (0 to 9%). Rare instances of dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea (4 to 12%), constipation (2 to 6%); and rarely, dry mouth,

anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency (2 to 6%); and rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar.

OVERDOSAGE

Signs and Symptoms:

Vomiting, muscular hypotonia, drowsiness, accommodation disorders, coma, respiratory depression and seizures.

Treatment:

In the alert patient, empty the stomach promptly by induced emesis followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Maintain adequate respiratory exchange, do not use respiratory stimulants.

DOSAGE AND ADMINISTRATION

The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40 to 80 mg daily).

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days

10 mg t.i.d. for 3 days

15 mg t.i.d. for 3 days

20 mg t.i.d. for 3 days

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.).

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see **WARNINGS,** Abrupt Drug Withdrawal).

HOW SUPPLIED

Baclofen Tablets, USP 10 mg are white to off-white, oval shaped and scored. The upper

layer is debossed “2265”. The lower layer is debossed “V”; and supplied as follows:

- Bottles of 100: NDC-0603-2406-21
- Bottles of 500: NDC 0603-2406-28
- Bottles of 1000: NDC 0603-2406-32

Baclofen Tablets, USP 20 mg are white to off-white, capsule shaped and scored. The upper layer is debossed “2266”. The lower layer is debossed “V”; and are supplied as follows:

- Bottles of 100: NDC-0603-2407-21
- Bottles of 500: NDC-0603-2407-28
- Bottles of 1000: NDC 0603-2407-32

Dispense in a tight container with child-resistant closure.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Manufactured for:
Endo USA
Malvern, PA 19355 U.S.A.
Made in India

Neutral Code: TN/DRUGS/TN00002121

OS2406H-01-74-04

Revised: 11/2024

PRINCIPAL DISPLAY PANEL - 10 mg

PRINCIPAL DISPLAY PANEL - 20 mg

BACLOFEN

baclofen tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0603-2406
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BACLOFEN (UNII: H789N3FKE8) (BACLOFEN - UNII:H789N3FKE8)	BACLOFEN	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	white (off-white)	**Score**	2 pieces
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	2265;V
Contains			

Packaging				
			Marketing Start	**Marketing End**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0603-2406-02	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	03/31/2016
2	NDC:0603-2406-21	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	
3	NDC:0603-2406-28	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	
4	NDC:0603-2406-32	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	01/31/2027
5	NDC:0603-2406-30	2500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	10/31/2017

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077068	08/30/2005	

BACLOFEN

baclofen tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0603-2407
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BACLOFEN (UNII: H789N3FKE8) (BACLOFEN - UNII:H789N3FKE8)	BACLOFEN	20 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	white (off-white)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	16mm
Flavor		**Imprint Code**	2266;V
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0603-2407-21	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	
2	NDC:0603-2407-28	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	
3	NDC:0603-2407-32	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/30/2005	01/31/2026

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077068	08/30/2005	

Labeler - Par Health USA, LLC (119547712)

Revised: 11/2024 Par Health USA, LLC

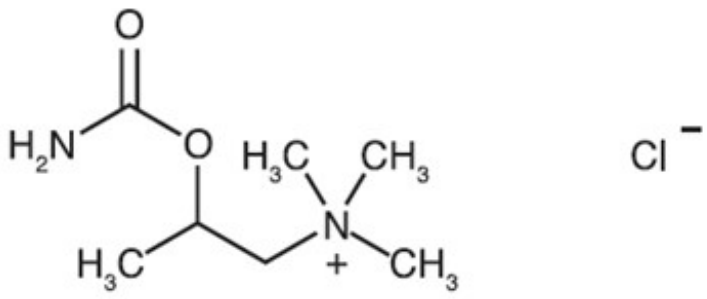
BETHANECHOL CHLORIDE- bethanechol chloride tablet
Heritage Pharma Labs Inc. d/b/a Avet Pharmaceuticals Labs Inc.

Bethanechol Chloride Tablets, USP
Rx only

DESCRIPTION

Bethanechol chloride, a cholinergic agent, is a synthetic ester which is structurally and pharmacologically related to acetylcholine.

It is designated chemically as 2-[(aminocarbonyl)oxy]-*N, N, N,*-trimethyl-1-propanaminium chloride. Its molecular formula is $C_7H_{17}ClN_2O_2$ and its structural formula is:



It is a white, hygroscopic crystalline powder having a slight amine-like odor, freely soluble in water, and has a molecular weight of 196.68.

Each tablet for oral administration contains 5 mg, 10 mg, 25 mg or 50 mg bethanechol chloride, USP. Tablets also contain the following inactive ingredients: lactose monohydrate, silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and povidone.

CLINICAL PHARMACOLOGY

Bethanechol chloride acts principally by producing the effects of stimulation of the parasympathetic nervous system. It increases the tone of the detrusor urinae muscle, usually producing a contraction sufficiently strong to initiate micturition and empty the bladder. It stimulates gastric motility, increases gastric tone and often restores impaired rhythmic peristalsis.

Stimulation of the parasympathetic nervous system releases acetylcholine at the nerve endings. When spontaneous stimulation is reduced and therapeutic intervention is required, acetylcholine can be given, but it is rapidly hydrolyzed by cholinesterase and its effects are transient. Bethanechol chloride is not destroyed by cholinesterase and its effects are more prolonged than those of acetylcholine.

Effects on the GI and urinary tracts sometimes appear within 30 minutes after oral

administration of bethanechol chloride, but more often 60 to 90 minutes are required to reach maximum effectiveness. Following oral administration, the usual duration of action of bethanechol is one hour, although large doses (300 to 400 mg) have been reported to produce effects for up to six hours. Subcutaneous injection produces a more intense action on bladder muscle than does oral administration of the drug.

Because of the selective action of bethanechol, nicotinic symptoms of chlolinergic stimulation are usually absent or minimal when orally or subcutaneously administered in therapeutic doses, while muscarinic effects are prominent. Muscarinic effects usually occur within 5 to 15 minutes after subcutaneous injection, reach a maximum in 15 to 30 minutes, and disappear within two hours. Doses that stimulate micturition and defecation and increase peristalsis do not ordinarily stimulate ganglia or voluntary muscles. Therapeutic test doses in normal human subjects have little effect on heart rate, blood pressure or peripheral circulation.

Bethanechol chloride does not cross the blood-brain barrier because of its charged quaternary amine moiety. The metabolic rate and mode of excretion of the drug have not been elucidated.

A clinical study (Diokno, A.C.; Lapides, J.; Urol 10: 23-24, July 1977) was conducted on the relative effectiveness of oral and subcutaneous doses of bethanechol chloride on the stretch response of bladder muscle in patients with urinary retention. Results showed that 5 mg of the drug given subcutaneously stimulated a response that was more rapid in onset and of larger magnitude than an oral dose of 50 mg, 100 mg, or 200 mg. All the oral doses, however, had a longer duration of effect than the subcutaneous dose. Although the 50 mg oral dose caused little change in intravesical pressure in this study, this dose has been found in other studies to be clinically effective in the rehabilitation of patients with decompensated bladders.

INDICATIONS AND USAGE

Bethanechol chloride is indicated for the treatment of acute postoperative and postpartum nonobstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention.

CONTRAINDICATIONS

Hypersensitivity to bethanechol chloride tablets, hyperthyroidism, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy and parkinsonism.

Bethanechol chloride should not be employed when the strength or integrity of the gastrointestinal or bladder wall is in question, or in the presence of mechanical obstruction; when increased muscular activity of the gastrointestinal tract or urinary bladder might prove harmful, as following recent urinary bladder surgery, gastrointestinal resection and anastomosis, or when there is possible gastrointestinal obstruction; in bladder neck obstruction, spastic gastrointestinal disturbances, acute inflammatory lesions of the gastrointestinal tract, or peritonitis; or in marked vagotonia.

PRECAUTIONS

General

In urinary retention, if the sphincter fails to relax as bethanechol contracts the bladder, urine may be forced up the ureter into the kidney pelvis. If there is bacteriuria, this may cause reflux infection.

Information for Patients

Bethanechol chloride tablets should preferably be taken one hour before or two hours after meals to avoid nausea or vomiting. Dizziness, lightheadedness or fainting may occur, especially when getting up from a lying or sitting position.

Drug Interactions

Special care is required if this drug is given to patients receiving ganglion blocking compounds because a critical fall in blood pressure may occur. Usually, severe abdominal symptoms appear before there is such a fall in the blood pressure.

Carcinogeneis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the effects upon fertility, mutagenic or carcinogenic potential of bethanechol chloride.

Pregnancy

Teratogenic effects: Pregnancy Category C

Animal reproduction studies have not been conducted with bethanechol chloride. It is also not known whether bethanechol chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Bethanechol chloride should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions from bethanechol chloride 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions are rare following oral administration of bethanechol, but are more common following subcutaneous injection. Adverse reactions are more likely to occur when dosage is increased.

The following adverse reactions have been observed: *Body as a Whole:* malaise; *Digestive:* abdominal cramps or discomfort, colicky pain, nausea and belching, diarrhea, borborygmi, salivation; *Renal:* urinary urgency; *Nervous System:* headache; *Cardiovascular:* a fall in blood pressure with reflex tachycardia, vasomotor response; *Skin:* flushing producing a feeling of warmth, sensation of heat about the face, sweating; *Respiratory:* bronchial constriction, asthmatic attacks; *Special Senses:* lacrimation, miosis.

Causal Relationship Unknown: The following adverse reactions have been reported, and a causal relationship to therapy with bethanechol has not been established: *Body as a whole:* malaise; *Nervous System:* seizures.

To report SUSPECTED ADVERSE REACTIONS, contact Avet Pharmaceuticals Inc. at 1-866-901-DRUG (3784) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Early signs of overdosage are abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating, nausea, and vomiting.

Atropine Sulfate is a specific antidote. The recommended dose for adults is 0.6 mg. Repeat doses can be given every two hours, according to clinical response. The recommended dosage in infants and children up to 12 years of age is 0.01 mg/kg (to a maximum single dose of 0.4 mg) repeated every two hours as needed until the desired effect is obtained or adverse effects of atropine preclude further usage. Subcutaneous injection of atropine is preferred except in emergencies when the intravenous route may be employed.

The oral LD_{50} of bethanechol chloride is 1510 mg/kg in the mouse.

DOSAGE AND ADMINISTRATION

Dosage must be individualized, depending on the type and severity of the condition to be treated.

Preferably give the drug when the stomach is empty. If taken soon after eating, nausea and vomiting may occur.

The usual adult oral dose ranges from 10 to 50 mg three or four times a day. The minimum effective dose is determined by giving 5 to 10 mg initially and repeating the same amount at hourly intervals until satisfactory response occurs, or until a maximum of 50 mg has been given. The effects of the drug sometimes appear within 30 minutes and are usually maximal within 60 to 90 minutes. The drug effects persist for about one hour.

If necessary, the effects of the drug can be abolished promptly by atropine (see **OVERDOSAGE**).

HOW SUPPLIED

Bethanechol Chloride Tablets, USP

5 mg - White, round, flat-faced beveled edge tablets debossed "934" on one side and score line on the other side.

NDC 23155-934-01 Bottles of 100

10 mg - White, round, flat-faced beveled edge tablets debossed "935" on one side and score line on the other side.

NDC 23155-935-01 Bottles of 100

25 mg - White, round, flat-faced beveled edge tablets debossed “936” on one side and score line on the other side.

NDC 23155-936-01 Bottles of 100

50 mg - White, round, flat-faced beveled edge tablets debossed “937” on one side and score line on the other side.

NDC 23155-937-01 Bottles of 100

Dispense in a tight container as defined in the USP.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Distributed by:

Avet Pharmaceuticals Inc.

East Brunswick, NJ 08816

1-866-901-DRUG (3784)

Revised: 03/2025

PRINCIPAL DISPLAY PANEL

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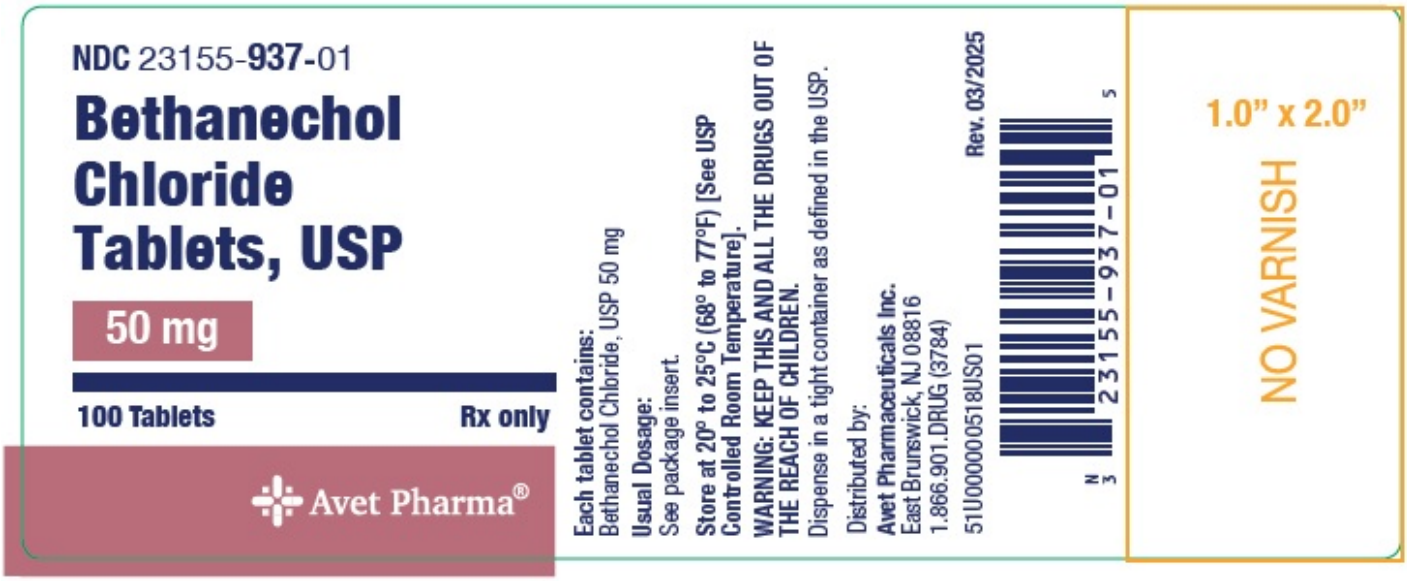


BETHANECHOL CHLORIDE

bethanechol chloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:23155-934
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BETHANECHOL CHLORIDE (UNII: H4QBZ2LO84) (BETHANECHOL - UNII:004F72P8F4)	BETHANECHOL CHLORIDE	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE (UNII: FZ989GH94E)	

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	934
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:23155-934-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/30/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091256	06/30/2025	

BETHANECHOL CHLORIDE

bethanechol chloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:23155-935
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BETHANECHOL CHLORIDE (UNII: H4QBZ2LO84) (BETHANECHOL - UNII:004F72P8F4)	BETHANECHOL CHLORIDE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE (UNII: FZ989GH94E)	

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	935
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:23155-935-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/30/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091256	06/30/2025	

BETHANECHOL CHLORIDE

bethanechol chloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:23155-936
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BETHANECHOL CHLORIDE (UNII: H4QBZ2LO84) (BETHANECHOL - UNII:004F72P8F4)	BETHANECHOL CHLORIDE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE (UNII: FZ989GH94E)	

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	936
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:23155-936-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/30/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091256	06/30/2025	

BETHANECHOL CHLORIDE

bethanechol chloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:23155-937
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BETHANECHOL CHLORIDE (UNII: H4QBZ2LO84) (BETHANECHOL - UNII:004F72P8F4)	BETHANECHOL CHLORIDE	50 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE (UNII: FZ989GH94E)	

Product Characteristics

Color	white	**Score**	2 pieces
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	937
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:23155-937-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/30/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091256	06/30/2025	

Labeler - Heritage Pharma Labs Inc. d/b/a Avet Pharmaceuticals Labs Inc. (780779901)

Registrant - Heritage Pharma Labs Inc. d/b/a Avet Pharmaceuticals Labs Inc. (189630168)

Establishment

Name	Address	ID/FEI	Business Operations
Heritage Pharma Labs Inc. d/b/a Avet Pharmaceuticals Labs Inc.		189630168	analysis(23155-934, 23155-935, 23155-936, 23155-937) , label(23155-934, 23155-935, 23155-936, 23155-937) , manufacture(23155-934, 23155-935, 23155-936, 23155-937) , pack(23155-934, 23155-935, 23155-936, 23155-937)

PRODUCT MONOGRAPH

PrAPO-SOTALOL

Sotalol Tablets BP

as Sotalol Hydrochloride

80 mg and 160 mg

ANTIARRHYTHMIC

APOTEX INC.
150 Signet Drive
Weston, Ontario
M9L 1T9

DATE OF REVISION:
July 22, 2022

Submission Control # 265824

PRODUCT MONOGRAPH

[Pr]APO-SOTALOL

Sotalol Tablets BP

80 mg and 160 mg

THERAPEUTIC CLASSIFICATION

Antiarrhythmic

ACTIONS AND CLINICAL PHARMACOLOGY

Sotalol hydrochloride has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol hydrochloride is a racemic mixture of d- and l-sotalol. Both isomers have similar Class III antiarrhythmic effects, while the l-isomer is responsible for virtually all of the beta- blocking activity. APO-SOTALOL is non-cardio selective and is not associated with partial agonist or membrane stabilizing activity. Whereas significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are seen at daily doses of 160 mg and above. The antiarrhythmic activity of APO-SOTALOL appears to be primarily due to the drug's Class III property, based on animal models.

Pharmacologically, in addition to its antiarrhythmic properties, sotalol hydrochloride also has antihypertensive and antianginal properties.

Electrophysiology

Sotalol hydrochloride prolongs the plateau phase of the cardiac action potential in the isolated myocyte, as well as in isolated tissue preparations of ventricular and atrial muscle (Class III activity). In intact animals it slows heart rate, decreases A-V nodal conduction and increases the refractory periods of atrial and ventricular muscle and conduction tissue.
In man, the Class II (beta-blockade) electrophysiological effects of APO-SOTALOL are manifested by increased sinus cycle length, decreased AV nodal conduction and increased AV nodal refractoriness. The Class III electrophysiological effects in man include prolongation of the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrioventricular accessory pathways (where present) in both the anterograde and retrograde directions. With oral doses of 160 to 640 mg/day, the surface ECG shows dose-related mean increases of 40-100 msec in QT and 10-40 msec in QT_c. No significant alteration in QRS interval is observed.

In a small study (n=25) of patients with implanted defibrillators treated concurrently with sotalol hydrochloride, the average defibrillatory threshold was 6 joules (range 2-15 joules) compared to a mean of 16 joules for a non-randomized comparative group primarily receiving amiodarone.

In a randomized clinical trial [Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial] comparing choice of antiarrhythmic therapy by PES suppression versus Holter monitor selection (in each case followed by treadmill exercise testing) in patients with a history of sustained VT/VF who were also inducible by PES, the effectiveness acutely and chronically of sotalol hydrochloride was compared with 6 other drugs (procainamide, quinidine, mexiletine, propafenone, imipramine and pirmenol). Overall response, limited to first randomized drug, was 39% for APO-SOTALOL and 30% for the pooled other drugs. Acute response rate for first drug randomized using suppression of PES induction was 36% for sotalol hydrochloride versus a mean of 13% for the other drugs. Using the Holter monitoring endpoint (complete suppression of sustained VT, 90% suppression of NSVT, 80% suppression of VPC pairs, and at least 70% suppression of VPC's), sotalol hydrochloride yielded 41% response versus 45% for the other drugs combined. Among responders placed on long-term therapy identified acutely as effective (by either PES or Holter), sotalol hydrochloride, when compared to the pool of other drugs, had the lowest two-year mortality (13% versus 22%), the lowest two-year VT recurrence rate (30% versus 60%), and the lowest withdrawal rate (38% versus about 75-80%). The most commonly used doses of sotalol hydrochloride in this trial were 320 - 480 mg/day (66% of patients), with 16% receiving 240 mg/day or less and 18% receiving 640 mg or more.

It cannot be determined, however, in the absence of a controlled comparison of sotalol hydrochloride versus no pharmacologic treatment (e.g., in patients with implanted defibrillators) whether APO-SOTALOL response causes improved survival or identifies a population with a good prognosis.

Hemodynamics

In a study of systemic hemodynamic function measured invasively in 12 patients with a mean left ventricular (LV) ejection fraction of 37% and ventricular tachycardia (9 sustained and 3 non-sustained), a median dose of 160 mg twice daily of sotalol hydrochloride produced a 28% reduction in heart rate and a 24% decrease in cardiac index at 2 hours post-dosing at steady-state. Concurrently, systemic vascular resistance and stroke volume showed non-significant increases of 25% and 8%, respectively. Pulmonary capillary wedge pressure increased significantly from 6.4 mmHg to 11.8 mmHg in the 11 patients who completed the study. One patient was discontinued because of worsening congestive heart failure. Mean arterial pressure, mean pulmonary artery pressure and stroke work index did not significantly change. Exercise and isoproterenol induced tachycardia are antagonized by sotalol hydrochloride and total peripheral resistance increases by a small amount.

In hypertensive patients, sotalol hydrochloride produces significant reductions in both systolic and diastolic blood pressures. Although APO-SOTALOL is usually well tolerated hemodynamically, caution should be exercised in patients with marginal cardiac compensation as deterioration in cardiac performance may occur (see WARNINGS: Congestive Heart Failure).

Pharmacokinetics

In Healthy Subjects: The oral bioavailability of sotalol hydrochloride is 90 - 100%. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state

plasma concentrations are attained within 2-3 days. Over the dosage range of 160-640 mg/day, sotalol hydrochloride displays dose proportionality with respect to plasma concentrations. Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 7 - 15 hours.

Sotalol hydrochloride does not bind to plasma proteins and is not metabolized. The pharmacokinetics of the d and l enantiomers of APO-SOTALOL are essentially identical. APO-SOTALOL crosses the blood brain barrier poorly. In one study, mean cerebrospinal fluid concentrations following a single oral dose ranged from 5% to 28% of those observed in plasma.

In Renally-Impaired Patients: Excretion is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in renal impairment (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

In Hepatically-Impaired Patients: Since sotalol hydrochloride is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol hydrochloride.

In Elderly Patients: Age per se does not significantly alter the pharmacokinetics of sotalol hydrochloride, but impaired renal function in elderly patients can increase the terminal elimination half-life, resulting in increased drug accumulation.

Effect of Food: When sotalol hydrochloride was administered with a standard meal, the absorption was reduced by approximately 20% compared to that in the fasting state.
A blinded, randomized, cross-over, single-dose bioavailability study was conducted in 18 healthy male volunteers to compare the bioavailability of APO-SOTALOL (160 mg) tablets to Sotacor® (160 mg) tablets. The pharmacokinetic results are listed in the table that follows.

Summary Table of the Sotalol HCl 160 mg Tablet
Comparative Bioavailability Data
(Dose: 160 mg) (From measured data)

Geometric Mean*
Arithmetic Mean (CV%)**

Parameter	**APO-Sotalol**	**Sotacor®**	**Ratio of Means**
AUC_T	16237	16523	98.3
(ng•hr/mL)	16729 (22)	16786 (19)	
AUC_I	16703	16989	98.3
(ng•hr/mL)	17186 (22)	17241 (18)	
C_{max}	1414	1420	99.5
(ng/mL)	1459 (24)	1450 (21)	
T_{max} (hr)	3.0 (0.74)	3.4 (0.61)	
$t_{1/2}$ (hr)	10.8 (1.59)	10.7 (1.67)	

*The geometric means are presented for AUC_T, AUC_I and C_{max} parameters
**For T_{max} and $t_{1/2}$ parameters, the arithmetic means (SD) are presented

These results demonstrate the bioequivalence of these two formulations.

INDICATIONS AND CLINICAL USE

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

APO-SOTALOL (sotalol hydrochloride) is indicated for the treatment of documented life-threatening ventricular arrhythmias such as sustained ventricular tachycardia. APO-SOTALOL may also be used for the treatment of patients with documented symptomatic ventricular arrhythmias when the symptoms are of sufficient severity to require treatment. Because of the proarrhythmic effects of APO-SOTALOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risks.

For patients with sustained ventricular tachycardia, APO-SOTALOL therapy should be initiated in the hospital. Hospitalization may also be required for certain other patients depending on their cardiac status and underlying cardiac disease.

In view of the proarrhythmic effects of APO-SOTALOL, its use in patients with hypertension or angina pectoris is not recommended unless they also require APO-SOTALOL for the treatment of ventricular arrhythmias.

CONTRAINDICATIONS

APO-SOTALOL (sotalol hydrochloride) is contraindicated in patients with bronchial asthma, allergic rhinitis, severe sinus node dysfunction, sinus bradycardia, second and third degree AV block (unless a functioning pacemaker is present), congenital or acquired long QT syndrome, cardiogenic shock, severe or uncontrolled congestive heart failure, hypokalemia, anesthesia with agents that produce myocardial depression and previous evidence of hypersensitivity to APO-SOTALOL.

WARNINGS

Mortality: The results of the Cardiac Arrhythmia Suppression Trial (CAST) in post-myocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in non-fatal cardiac arrest rate in patients treated with encainide or flecainide compared with a matched placebo-treated group. CAST was continued using a revised protocol with the moricizine and placebo arms only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine treated group. The applicability of these results to other populations or other antiarrhythmic agents is uncertain, but at present it is prudent to consider these results when using any antiarrhythmic agent.

Proarrhythmia: APO-SOTALOL (sotalol hydrochloride) may cause new or worsen existing arrhythmias. Such proarrhythmic effects range from an increase in frequency of premature

ventricular contractions to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes. It is therefore essential that each patient administered APO-SOTALOL be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to APO-SOTALOL supports continued treatment. Sotalol hydrochloride, like some antiarrhythmic agents, has been associated with a specific form of arrhythmia, torsade de pointes, which is defined as a polymorphic ventricular tachycardia with prolongation of the QT interval and QRS complexes of changing amplitude that appear to twist around the isoelectric axis. Torsades have been observed more frequently in patients with an elevated baseline QT (>430 msec), on-therapy QT of >500 msec, bradycardia (heart rate <50 bpm), hypokalemia and hypomagnesemia (see WARNINGS, Electrolyte Disturbances) and congestive heart failure. Because of the variable temporal recurrence of arrhythmias, it is not always possible to distinguish between a new or aggravated arrhythmic event and lack of efficacy. Thus, the incidence of drug-related events cannot be precisely determined and the rates of occurrence provided below must be considered approximations. It should be noted that drug-induced arrhythmias may often not be identified until late after starting the drug because of infrequent monitoring. Due to the possibility of proarrhythmic effects, APO-SOTALOL is not recommended for the treatment of patients with asymptomatic premature contractions (see INDICATIONS AND CLINICAL USE).

Overall in clinical trials with APO-SOTALOL, 4.3% of 3257 patients experienced a new or worsened ventricular arrhythmia. Of this 4.3%, new or worsened sustained ventricular tachycardia was reported in approximately 1% of patients, and torsade de pointes in 2.4%. Additionally, in approximately 1% of patients, deaths were considered possibly drug-related; such cases, although difficult to evaluate, may have been associated with proarrhythmic events. In patients with a history of sustained ventricular tachycardia, the incidence of torsade de pointes was 4%, and worsened VT was approximately 1%; in patients with other, less serious, ventricular arrhythmias and supraventricular arrhythmias, the incidence of torsade de pointes was 1% and 1.4%, respectively.

As shown in the table below, torsade de pointes arrhythmias as well as the prolongation of QT (QT_c) interval were dose related.

Percent Incidence of Torsade de Pointes and Mean QT_c Interval by Dose for Patients with Sustained VT/VF		
Daily Dose (mg)	Incidence of Torsade de Pointes	Mean QT_c* (msec)
80	0 (69)	463 (17)
160	0.5 (832)	467 (181)
320	1.6 (835)	473 (344)
480	4.4 (459)	483 (234)
640	3.7 (324)	490 (185)
>640	5.8 (103)	512 (62)
( ) Number of patients assessed; * Highest on-therapy value		

In addition to dose and presence of sustained VT, other risk factors for torsade de pointes were gender (females had a higher incidence), excessive prolongation of the QT_c interval (see table

below) and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure appear to have the highest risk for serious proarrhythmia (7%). Of the patients experiencing torsade de pointes, approximately two-thirds spontaneously reverted to their baseline rhythm. The others were either converted electrically (D/C cardioversion or overdrive pacing) or treated with other drugs (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). It is not possible to determine whether some sudden deaths represented episodes of torsade de pointes, but in some instances sudden death did follow a documented episode of torsade de pointes. Although APO-SOTALOL therapy was discontinued in most patients experiencing torsade de pointes, 17% were continued on a lower dose. Nonetheless, APO-SOTALOL should be used with particular caution if the QT_c is greater than 500 msec on- therapy and serious consideration should be given to reducing the dose or discontinuing therapy when the QT_c exceeds 550 msec. Due to the multiple risk-factors associated with torsade de pointes, however, caution should be exercised regardless of the QT_c interval. The table below relates the incidence of torsade de pointes to on-therapy QT_c and change in QT_c from baseline. It should be noted, however, that the highest on-therapy QT_c was in many cases the one obtained at the time of the torsade de pointes event, so that the table overstates the predictive value of a high QT_c.

Relationship Between QT_C Interval Prolongation and Torsade de Pointes

On-Therapy QTC Interval (msec)	Incidence of Torsade de Pointes
<500	1.3% (1787)
500 – 525	3.4% (236)
525 – 550	5.6% (125)
>550	10.8% (157)

Change in QTC Interval from Baseline (msec)	Incidence of Torsade de Pointes
<65	1.6% (1516)
65 - 80	3.2% (158)
80 - 100	4.1% (146)
100 - 130	5.2% (115)
>130	7.1% (99)

( ) Number of patients assessed.

Proarrhythmic events must be anticipated not only on initiating therapy, but with every upward dose adjustment. Proarrhythmic events most often occur within 7 days of initiating therapy or of an increase in dose; 75% of serious proarrhythmias (torsade de pointes and worsened VT) occurred within 7 days of initiating APO-SOTALOL therapy, while 60% of such events occurred within 3 days of initiation or a dosage change. Initiating therapy at 80 mg b.i.d. with gradual upward dose titration and appropriate evaluations for efficacy (e.g., PES or Holter) and safety (e.g., QT interval, heart rate and electrolytes) prior to dose escalation should reduce the risk of proarrhythmia. Avoiding excessive accumulation of APO-Sotalol in patients with diminished renal function, by appropriate dose reduction, should also reduce the risk of proarrhythmia (see DOSAGE AND ADMINISTRATION).

Electrolyte Disturbances: APO -SOTALOL should not be used in patients with hypokalemia or hypomagnesemia prior to correction of such imbalance, as these conditions can exaggerate the degree of QT prolongation and increase the potential for torsade de pointes. The serum

electrolytes must be monitored regularly and more frequently if diuretics are used concomitantly. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or patients receiving concomitant diuretics.

Congestive Heart Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure (CHF), and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Moreover, patients with CHF have a higher risk of torsade de pointes (see WARNINGS, Proarrhythmia).

In patients with controlled CHF, APO-SOTALOL should be administered cautiously. The positive inotropic action of digitalis may be reduced when the two drugs are used concomitantly. Both digitalis and sotalol slow AV conduction. If cardiac failure continues despite adequate digitalization, APO-SOTALOL should be discontinued.

In patients without a history of heart failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. At the first sign of impending heart failure, appropriate therapy must be established and consideration should be given to discontinuation of treatment with APO-SOTALOL.

In clinical trials, new or worsened congestive heart failure (CHF) occurred in 3.3% (n=3257) of patients and led to discontinuation in approximately 1% of patients receiving APO-SOTALOL. The incidence was higher in patients presenting with sustained ventricular tachycardia/fibrillation (4.6%, n=1363), or a prior history of heart failure (7.3%, n=696). Based on a life-table analysis, the one-year incidence of new or worsened CHF was 3% in patients without a prior history and 10% in patients with a prior history of CHF. NYHA Classification was also closely associated to the incidence of new or worsened heart failure in patients receiving APO-SOTALOL (1.8% in 1395 Class I patients, 4.9% in 1254 Class II patients and 6.1% in 278 Class III or IV patients).

Conduction Disturbances: Excessive prolongation of the QT interval (>550 msec) can promote serious arrhythmias and should be avoided (see Proarrhythmia). Sinus bradycardia (heart rate less than 50 bpm) occurred in 13% of patients receiving Sotalol hydrochloride in clinical trials, and led to discontinuation in about 3% of patients. Bradycardia itself increases the risk of torsade de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

Recent Myocardial Infarction: Caution should be exercised when APO-SOTALOL is given to patients with recent myocardial infarction. Experience in the use of sotalol hydrochloride in the early stage of recovery from acute myocardial infarction is limited and, at least at high initial doses, not reassuring. In the first 2 weeks following acute myocardial infarction, particular caution is advised. Careful dose titration is especially important, particularly in patients with impaired ventricular function.

In a double-blind, placebo-controlled secondary prevention trial in 1456 post-infarction patients who did not necessarily have ventricular arrhythmias, Sotalol hydrochloride was given as a non-titrated dose of 320 mg once daily. The results did not suggest an adverse effect on survival;

however, there was a suggestion of excess mortality (3% on sotalol hydrochloride versus 2% on placebo) during the first ten days of the trial. In another trial, where high doses of sotalol hydrochloride (320 mg twice daily) were given to a small number of high-risk post-infarction patients (n=17 randomized to APO-SOTALOL), there were four fatalities and three serious hemodynamic/electrical adverse events within two weeks of initiating sotalol hydrochloride.

Abrupt Cessation of Therapy: Patients should be warned against abrupt interruption or discontinuation of APO-SOTALOL. Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy. There have been occasional reports of severe exacerbation of angina pectoris, ventricular arrhythmias and in some cases myocardial infarction following abrupt discontinuation of beta blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, it is prudent when discontinuing chronically administered APO-SOTALOL, particularly in patients with ischemic heart disease, to carefully monitor the patient and to discontinue APO-SOTALOL in a stepwise manner or consider the temporary use of an alternate beta-blocker if appropriate. If possible, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. If angina markedly worsens or acute coronary insufficiency develops, appropriate therapy should be instituted promptly. Because coronary artery disease is common and may be unrecognized in patients receiving

APO-SOTALOL, abrupt discontinuation in patients with arrhythmias may unmask latent coronary insufficiency.

Anaphylaxis: While taking beta blockers, patients with a history of anaphylactic reactions to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic.

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other hand, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation ofbronchospasm.

Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Non-Allergic Bronchospasm (e.g. Chronic Bronchitis and Emphysema): **Patients with bronchospastic diseases should in general not receive beta-blockers**. It is prudent, if APO-SOTALOL is to be administered, to use the smallest effective dose, so that inhibition of bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors may be minimized.

Sick Sinus Syndrome: APO-SOTALOL should be used only with extreme caution in patients with sick sinus syndrome associated with symptomatic arrhythmias, because it may cause sinus bradycardia, sinus pauses or sinus arrest.

Skin Rashes and Oculomucocutaneous Syndrome: Various skin rashes and conjunctival xerosis have been reported with beta blockers, including sotalol hydrochloride. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic-blocking agent (practolol). This syndrome has not been observed with sotalol hydrochloride. Physicians, however, should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Thyrotoxicosis: In patients with thyrotoxicosis, APO-SOTALOL may mask the clinical signs of hyperthyroidism or its complications and give a false impression of improvement. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of APO-SOTALOL which might be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

PRECAUTIONS

Renal Impairment: Renal function tests should be carried out at appropriate intervals. Caution should be observed in patients with impaired renal function since APO-SOTALOL (sotalol hydrochloride) is eliminated mainly via the kidneys through glomerular filtration and to a small degree by tubular secretion. There is a direct relationship between renal function, as measured by serum creatinine or creatinine clearance, and the elimination rate of APO-Sotalol. Guidance for dosing in conditions of renal impairment can be found under DOSAGE AND ADMINISTRATION.

Diabetes: APO-SOTALOL should be administered with caution to patients with history of spontaneous hypoglycemia or to patients with diabetes (especially labile diabetes) receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia; e.g. tachycardia.

Anesthesia: It is not advisable to withdraw beta-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using APO-SOTALOL with anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.).

Some patients receiving beta-adrenoceptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting the heart and maintaining the heart beat has also been reported.

In emergency surgery, since APO-Sotalol is a competitive antagonist at beta-adrenoceptor sites, its effects may be reversed, if required, by sufficient doses of such agonists as isoproterenol or noradrenaline.

Use in Pregnancy: There are no studies in pregnant women. Sotalol hydrochloride has been shown to cross the placenta, and is found in amniotic fluid. There has been a report of subnormal birth weight with sotalol hydrochloride. Therefore, APO-SOTALOL should be used during pregnancy only if the potential benefit outweighs the potential risk.

Use in Nursing Mothers: APO-SOTALOL has been reported to be present in human milk. Because of the potential for adverse reactions from APO-SOTALOL 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.

Use in Children: The safety and effectiveness of APO-SOTALOL in children have not been established.

Drug Interactions

Antiarrhythmics: Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide, and Class III drugs (e.g. amiodarone) are not recommended as concomitant therapy with APO-SOTALOL because of their potential to prolong refractoriness (see WARNINGS). There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics. Additive Class II effects would also be anticipated with the use of other beta-blocking agents concomitantly with APO-SOTALOL.

Drugs Prolonging the QT Interval: APO-SOTALOL should also be given with extreme caution in conjunction with other drugs known to prolong the QT interval, such as Class I and Class III antiarrhythmics, phenothiazines, tricyclic antidepressants, terfenadine, astemizole, erythromycin, lithium and liquid protein diets.

Digoxin: Single and multiple doses of sotalol hydrochloride do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol hydrochloride treated patients also receiving digoxin. It is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.

Calcium Blocking Drugs: APO-SOTALOL should be administered with caution in conjunction with calcium blocking drugs because of possible synergistic impairment of atrioventricular conduction and of ventricular function. Additionally, concomitant use of these drugs may have additive effects on blood pressure, possibly leading to hypotension.

Catecholamine-Depleting Agents: Concomitant use of catecholamine-depleting drugs, such as reserpine and guanethidine, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients treated with APO-SOTALOL plus a catecholamine-depletor should therefore be closely monitored for evidence of hypotension and/or marked bradycardia, which may produce syncope.

Insulin and Oral Hypoglycemics: Hypoglycemia and hyperglycemia may occur and the dosage of antidiabetic drugs should be adjusted accordingly (see PRECAUTIONS, Diabetes).

Clonidine: Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, the beta-blocker should be discontinued several days before the gradual withdrawal of clonidine.

Beta-2-Receptor Stimulants: Beta-agonists such as salbutamol, terbutaline and isoprenaline may have to be administered in increased dosages when used concomitantly with APO-SOTALOL.

ADVERSE REACTIONS

During premarketing trials, 3186 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral sotalol hydrochloride, of whom 2451 received the drug for at least two weeks. The most important adverse effects are torsade de pointes and other serious new ventricular arrhythmias (see WARNINGS), occurring at rates of almost 4% and 1%, respectively, in the VT/VF population. Overall, discontinuation because of unacceptable side effects was necessary in 17% of all patients in clinical trials, and in 13% of patients treated for at least two weeks. The most common adverse reactions leading to discontinuation of sotalol hydrochloride are as follows: fatigue 4%, bradycardia (<50 bpm) 3%, dyspnea 3%, proarrhythmia 3%, asthenia 2% and dizziness 2%. Occasional reports of elevated serum liver enzymes have occurred with APO-Sotalol therapy but no cause and effect relationship has been established.

One case of peripheral neuropathy which resolved on discontinuation of APO-Sotalol and recurred when the patient was rechallenged with the drug was reported in an early dose tolerance study. Elevated blood glucose levels and increased insulin requirements can occur in diabetic patients.

The following table lists as a function of dosage the most common (incidence of 2% or greater) adverse effects, regardless of relationship to therapy and the percent of patients discontinued due to the event, as collected from clinical trials involving 1292 patients with sustained VT/VF.

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
BODY AS A WHOLE							
Infection	1	2	2	2	3	4	<1
Fever	1	2	3	2	2	4	<1
Localized pain	1	1	2	2	2	3	<1
CARDIOVASCULAR							
Dyspnea	5	8	11	15	15	21	2
Bradycardia	8	8	9	7	5	16	2
Chest pain	4	3	10	10	14	16	<1
Palpitation	3	3	8	9	12	14	<1
Edema	2	2	5	3	5	8	1
ECG abnormal	4	2	4	2	2	7	1
Hypotension	3	4	3	2	3	6	2

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
Proarrhythmia	<1	<1	2	4	5	5	3
Syncope	1	1	3	2	5	5	1
Heart failure	2	3	2	2	2	5	1
Presyncope	1	2	2	4	3	4	<1
Peripheral vascular disorder	1	2	1	1	2	3	<1
Cardiovascular disorder	1	<1	2	2	2	3	<1
Vasodilation	1	<1	1	2	1	3	<1
AICD discharge	<1	2	2	2	2	3	<1
Hypertension	<1	1	1	1	2	2	<1
NERVOUS							
Fatigue	5	8	12	12	13	20	2
Dizziness	7	6	11	11	14	20	1
Asthenia	4	5	7	8	10	13	1
Lightheaded	4	3	6	6	9	12	1
Headache	3	2	4	4	4	8	<1
Sleep problem	1	1	5	5	6	8	<1
Perspiration	1	2	3	4	5	6	<1
Altered consciousness	2	3	1	2	3	4	<1
Depression	1	2	2	2	3	4	<1
Paresthesia	1	1	2	3	2	4	<1
Anxiety	2	2	2	3	2	4	<1
Mood change	<1	<1	1	3	2	3	<1
Appetite disorder	1	2	2	1	3	3	<1
Stroke	<1	<1	1	1	<1	1	<1
DIGESTIVE							
Nausea/vomiting	5	4	4	6	6	10	1
Diarrhea	2	3	3	3	5	7	<1
Dyspepsia	2	3	3	3	3	6	<1
Abdominal pain	<1	<1	2	2	2	3	<1
Colon problem	2	1	1	<1	2	3	<1
Flatulence	1	<1	1	1	2	2	<1
RESPIRATORY							
Pulmonary problem	3	3	5	3	4	8	<1
Upper respiratory tract	1	1	3	4	3	5	<1
problem Asthma	1	<1	1	1	1	2	<1
UROGENITAL							
Genitourinary disorder	1	0	1	1	2	3	<1
Sexual dysfunction	<1	1	1	1	3	2	<1
METABOLIC							
Abnormal lab value	1	2	3	2	1	4	<1
Weight change	1	1	1	<1	2	2	<1
MUSCULOSKELETAL							
Extremity pain	2	2	4	5	3	7	<1
Back pain	1	<1	2	2	2	3	<1

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
SKIN AND APPENDAGES Rash	2	3	2	3	4	5	<1
HEMATOLOGIC Bleeding	1	<1	1	<1	2	2	<1
SPECIAL SENSES Visual problem	1	1	2	4	5	5	<1
*Because patients are counted at each dose level tested, the "Any Dose" column cannot be determined by adding across the doses.							

Potential Adverse Effects

Marketing experience with sotalol hydrochloride showed an adverse experience profile similar to that described above from clinical trials. Voluntary reports since introduction include rare reports (less than one report per 10,000 patients) of: emotional lability, slightly clouded sensorium, incoordination, vertigo, paralysis, thrombocytopenia, eosinophilia, leukopenia, photosensitivity reaction, fever, pulmonary edema, hyperlipidemia, myalgia, pruritus, reversible alopecia.

Additional adverse effects have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia; and acute reversible syndrome characterized by disorientation for time and place, short-term memory loss and decreased performance on neuropsychometrics.

Allergic: Fever, combined with aching and sore throat, laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenia purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

Other: Peyronie's disease, Raynaud's phenomenon.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Intentional or accidental overdosage with sotalol hydrochloride has rarely resulted in death. The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia. In cases of massive intentional overdosage (2 - 16 grams) with sotalol hydrochloride, the following clinical findings were seen: hypotension, bradycardia, prolongation of QT interval, torsade de pointes, ventricular tachycardia, and premature ventricular complexes. If overdosage occurs, therapy with sotalol hydrochloride should be discontinued. Close monitoring of the electrocardiogram in patients with suspected APO-

SOTALOL intoxication is essential. Because of the lack of protein binding, hemodialysis is useful for reducing APO-SOTALOL plasma concentrations. Patients should be carefully observed until QTc intervals are normalized. Every effort should be made to correct promptly metabolic and electrolyte imbalances which might contribute to the initiation of ventricular arrhythmias (see WARNINGS).

If required, the following therapeutic measures are suggested:

1) Bradycardia: Atropine, another anticholinergic drug, a beta-adrenergic agonist or transvenous cardiac pacing.
2) Heart Block (second and third degree): Isoproterenol or transvenous cardiac pacemaker.
3) Congestive Heart Failure: Conventional therapy.
4) Hypotension: (Depending on associated factors) epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis (see PRECAUTIONS).
5) Bronchospasm: Aerosolized beta-2-receptor stimulant or aminophylline.
6) Hypoglycemia: Intravenous glucose.
7) Torsade de pointes: Epinephrine, magnesium sulphate, transvenous cardiac pacing, DC cardioversion.

It should be remembered that sotalol hydrochloride is a competitive antagonist of isoproterenol and, hence, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of APO-SOTALOL. However, the complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

APO-SOTALOL (sotalol hydrochloride), when used for the treatment of documented life-threatening ventricular arrhythmias, should be initiated and dose increased in a hospital with facilities for cardiac rhythm monitoring and assessment (see INDICATIONS AND CLINICAL USE). APO-SOTALOL should be administered only after appropriate clinical assessment, and the dosage of APO-SOTALOL must be individualized on the basis of therapeutic response and tolerance. The usefulness of monitoring plasma level for optimization of therapy has not been established. Proarrhythmic events can occur not only at the initiation of therapy, but also with each upward dosage adjustment.

Dosage of APO-SOTALOL should be adjusted gradually, allowing 2 - 3 days between dosing increments in order to attain steady-state plasma concentrations and to allow monitoring of QT intervals. Graded dose adjustment will help prevent the use of doses which are higher than necessary to control the arrhythmia. The recommended initial dose is 80 mg twice daily. If needed, this dose may be increased, after appropriate evaluation, to 240 or 320 mg/day. In most patients, a therapeutic response is obtained at a total daily dose of 160 to 320 mg/day, given in two divided doses. Some patients with life-threatening refractory arrhythmias may require doses as high as 480-640 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, in particular proarrhythmias. Because of the long elimination half-life of sotalol hydrochloride, dosing on more than a twice daily regimen is not usually necessary.

Patients experiencing bradycardia or hypotension on initial administration of APO -SOTALOL should be removed from therapy; APO-SOTALOL may be later reintroduced at a lower dose. A dose reduction may also be advisable to alleviate symptoms of weakness and dizziness in cases where blood pressure remains low after more than a month of therapy.

Renal Impairment: Because APO-SOTALOL is excreted predominantly in urine and its elimination half-life is prolonged in conditions of renal impairment, a longer duration of dosing is required to reach steady state. The dosing interval of APO-SOTALOL should then be modified, when creatinine clearance is <60 mL/min., as shown in the following table:

Creatinine Clearance (mL/min)	Dosing Interval (hours)
>60	12
30 - 60	24
10 - 30	36 - 48
<10	Dose should be individualized

Dose increases in renal impairment should only be done after administration of at least 5 or 6 doses at appropriate intervals.

Transfer to and from APO-SOTALOL: Based on theoretical considerations rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to APO-SOTALOL or from APO-SOTALOL to another antiarrhythmic agent, allow at least 3 to 4 half-lives to elapse for the drug being discontinued before starting the alternative drug at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

PHARMACEUTICAL INFORMATION

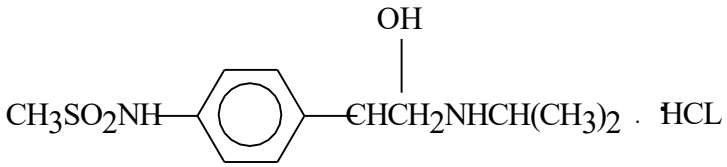
Drug Substance

Proper Name: Sotalol hydrochloride

Chemical Name(s): 1) Methanesulfonamide, *N*-[4-[1-hydroxy-2-[(1-methylethyl)-amino]ethyl]phenyl]-, monohydrochloride

2) 4'-[1-Hydroxy-2-(isopropyl-amino)ethyl]-methane-sulfonanilide monohydrochloride

Structural Formula:



Molecular Formula: $C_{12}H_{20}N_2O_3S \bullet HCl$

Molecular Weight: 308.82

Description: Sotalol hydrochloride is a white to pale cream, crystalline, odourless powder which has a melting point of 212 - 214ºC. It is freely soluble in water and methanol, and sparingly soluble in chloroform.

Composition
The non-medicinal ingredients in APO-SOTALOL are colloidal silicon dioxide, dextrates, indigotine (Blue #2), magnesium stearate and methylcellulose.

Stability and Storage Recommendations
Store at room temperature (15 to 30ºC). Protect from light.

AVAILABILITY OF DOSAGE FORMS

Each blue, capsule-shaped, biconvex tablet, identified "80" on one side and scored on the other, contains 80 mg of sotalol hydrochloride. Available in bottles of 100, 250, 500 and 1000.

Each blue, capsule-shaped, biconvex tablet, identified "160" on one side and scored on the other, contains 160 mg of sotalol hydrochloride. Available in bottles of 100, 250, 500 and 1000.

PHARMACOLOGY

In vitro, sotalol hydrochloride antagonized the chronotropic and inotropic effects of isoproterenol on isolated spontaneously beating atria and perfused cat heart, and antagonized the relaxant action of isoproterenol on the spontaneous contractions of the "diestrus" rat uterus, and the intrinsic tonus and histamine-induced spasms of the guinea pig.

In anesthetized dogs, sotalol hydrochloride administered intravenously had a negative inotropic

and chronotropic action.

Sotalol hydrochloride completely blocked the changes in heart rate, cardiac output, left ventricular work and total peripheral resistance induced by isoproterenol and had decreasing effects on respiration, blood pressure and heart rate similar to propranolol.

Sotalol hydrochloride reduced the mortality rate in dogs with ligation of a coronary artery, which was thought to be due to beta-blockade, suppressed the actinine, coronary artery ligation and hydrocarbon-epinephrine-induced arrhythmias and suppressed atrial flutter and restored normal sinus rhythm.

The ECG is not changed with the exception of a minor prolongation of the PR interval. Sotalol hydrochloride will inhibit isoproterenol-induced tachycardia and exercise tachycardia. In patients receiving right and left heart catheterization, the drug produced a significant reduction in heart rate and cardiac output, but stroke volume was unchanged. Systemic arterial and pulmonary pressures were not significantly altered, but indices of myocardial function were reduced. Nine patients with angina pectoris, studied at a constant treadmill speed, showed an increase in exercise time after sotalol hydrochloride i.v. 0.5 mg/kg of 80 to 165 seconds.

Sotalol hydrochloride has no local anesthetic action on rabbit eye or guinea pig skin at concentrations ranging from 0.1 to 6.4%. The intravenous injection of sotalol hydrochloride in anesthetized dogs caused reduction in pulmonary blood flow, increase in pulmonary vascular resistance and interference in the increase of pulmonary flow in response to isoproterenol, anoxia and electrical stimulation of thoracic sympathetic nerve.
In 13 patients suffering from obstructive lung disease, the administration of sotalol hydrochloride provoked a significant increase of the airway resistance and a decrease of the FEV. APO-Sotalol does not alter intraocular pressure.

TOXICOLOGY

Acute Toxicity

Species	Sex	No. of Animals	Route	LD_{50} (mg/kg)	No. of Deaths
Mice	M	50	Oral	2600	15
	M	130	i.p.	670 645	36
	M	40	i.v.	174	19
Rats	M	90	Oral	3450	13
	M	30	i.p.	680	-
Rabbits	M&F	12	Oral	1000	6
	M&F	12	i.v.	78	3
Dogs	M&F	6	Oral	50*	-
	M&F	18	i.p.	330	4
	M&F	24	i.v.	240	5
*Emesis occurred at doses of 100 and 200 mg/kg; LD_{50} could not be determined					

Signs of toxicity were: ataxia, labored respiration, loss of righting reflex, depression, hypoactivity, asphyxial movements and convulsions.

The following signs were also reported in some species: ptosis, increased respiratory depth, Straub's tail reaction, head and body shaking, emesis, bradycardia, cyanosis, relaxed nictitating membrane, moderate tearing, watery stools, weak heart beat, profuse salivation, coarse tremors and piloerection.

Chronic Toxicity

Species	Sex	Route of Administration	Dosage Regimen	Time Period	Toxicity Signs
Mice	F	Oral	500 mg/ kg/day	6 months	None
Rats	M&F	Oral	0,50,250, 1250 mg/ kg/day	1 year	Ataxia, depression, slightly depressed growth and food efficiency, increased spleen weight
Rats	M&F	Oral	0,75,275, 975 or 1000 mg/kg/day	1 year	Decrease in body weight gain (dose-related), increases in heart dimensions of male rats and cartilagenous metaplasia in heartsections
Dogs	M&F	Oral	0,5,15,45, 60 or 70 mg/kg/day	1 year	Decrease in heart rate (dose-related)

Reproductive Studies

The oral administration of sotalol hydrochloride of 500 mg/kg/day on days 3, 5, 7, 8, 10 and 12 of gestation in pregnant mice and of 100 mg/kg on day 6 through 16 in pregnant rabbits had no effect on the incidence of successful pregnancies, litter size, incidence of stillborn, weight of newborn, growth of newborn to weaning and post-natal survival.

Male rats fed 20 or 142 mg/kg of sotalol hydrochloride for 70 weeks exhibited no drug related decrease in reproductive performance.

Oral administration of 1000 mg/kg to male and female rats prior to mating had no adverse effect upon the fertility of female rats, the post-natal survival and development of the offspring. Female rats had fewer pups per litter than control rats. No evidence of teratogenesis was noted.

The continuous administration of sotalol hydrochloride to pregnant rats (20, 140 or 1000 mg/kg) and to pregnant rabbits (100, 150 or 225 mg/kg) during the critical period of organogenesis for each species had no teratogenic or embryotoxic effect on their offspring. In rats, 1000 mg/kg/day of sotalol hydrochloride increased the number of early resorptions, while at 14 times the maximum dose, no increase in early resorptions was noted.

Tumorigenic Tests

Sotalol hydrochloride, orally administered to mice at doses of 0, 100, 300 or 600 mg/kg/day for a period of 18 months in two different studies, did not show statistical differences in total or specific tumours when compared to control groups.

Sotalol hydrochloride, orally administered to rats at doses of 0, 137, or 275 mg/kg/day for a period of 18 months did not show statistical differences in the incidence of neoplasms, when compared to control groups.

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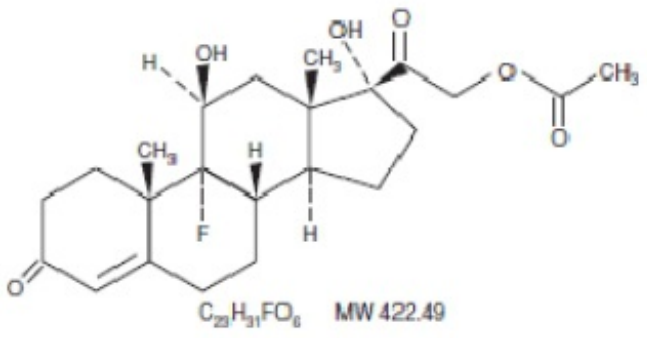
FLUDROCORTISONE ACETATE- fludrocortisone acetate tablet
West-ward Pharmaceutical Corp

Fludrocortisone Acetate Tablets, USP

Description

Fludrocortisone Acetate Tablets contain fludrocortisone acetate, a synthetic adrenocortical steroid possessing very potent mineralocorticoid properties and high glucocorticoid activity; it is used only for its mineralocorticoid effects. The chemical name for fludrocortisone acetate is 9-fluoro-11ß,17,21-trihydroxypregn-4-ene-3,20-dione 21-acetate; its structural formula is:



Fludrocortisone Acetate Tablets are available for oral administration as scored tablets providing 0.1 mg fludrocortisone acetate per tablet. Inactive ingredients: anhydrous lactose, corn starch, lactose monohydrate, magnesium stearate, sugar, and talc.

Clinical Pharmacology

Corticosteroids are thought to act, at least in part, by controlling the rate of synthesis of proteins. Although there are a number of instances in which the synthesis of specific proteins is known to be induced by corticosteroids, the links between the initial actions of the hormones and the final metabolic effects have not been completely elucidated.

The physiologic action of fludrocortisone acetate is similar to that of hydrocortisone. However, the effects of fludrocortisone acetate, particularly on electrolyte balance, but also on carbohydrate metabolism, are considerably heightened and prolonged. Mineralocorticoids act on the distal tubules of the kidney to enhance the reabsorption of sodium ions from the tubular fluid into the plasma; they increase the urinary excretion of both potassium and hydrogen ions. The consequence of these three primary effects together with similar actions on cation transport in other tissues appear to account for the entire spectrum of physiological activities that are characteristic of mineralocorticoids. In small oral doses, fludrocortisone acetate produces marked sodium retention and increased urinary potassium excretion. It also causes a rise in blood pressure, apparently because of these effects on electrolyte levels.

In larger doses, fludrocortisone acetate inhibits endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion; promotes the deposition of liver glycogen; and, unless protein intake is adequate, induces negative nitrogen balance.

The approximate plasma half-life of fludrocortisone (fluorohydrocortisone) is 3.5 hours or more and the biological half-life is 18 to 36 hours.

Indications and Usage

Fludrocortisone Acetate Tablets, 0.1 mg are indicated as partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

Contraindications

Corticosteroids are contraindicated in patients with systemic fungal infections and in those with a history of possible or known hypersensitivity to these agents.

Warnings

BECAUSE OF ITS MARKED EFFECT ON SODIUM RETENTION, THE USE OF FLUDROCORTISONE ACETATE IN THE TREATMENT OF CONDITIONS OTHER THAN THOSE INDICATED HEREIN IS NOT ADVISED.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. If an infection occurs during fludrocortisone acetate therapy, it should be promptly controlled by suitable antimicrobial therapy.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. However, since fludrocortisone acetate is a potent mineralocorticoid, both the dosage and salt intake should be carefully monitored in order to avoid the development of hypertension, edema, or weight gain. **Periodic checking of serum electrolyte levels is advisable during prolonged therapy; dietary salt restriction and potassium supplementation may be necessary.** All corticosteroids increase calcium excretion.

Patients should not be vaccinated against smallpox while on corticosteroid therapy. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of Fludrocortisone Acetate Tablets in patients with active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

Precautions

General

Adverse reactions to corticosteroids may be produced by too rapid withdrawal or by continued use of

large doses.

To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with fludrocortisone acetate and for a year afterwards.

There is an enhanced corticosteroid effect in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition being treated. A gradual reduction in dosage should be made when possible.

Psychic derangements may appear when corticosteroids are used. These may range from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Existing emotional instability or psychotic tendencies may also be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinemia.

Corticosteroids should be used with caution in patients with nonspecific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection. Corticosteroids should also be used cautiously in patients with diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Information for Patients

The physician should advise the patient to report any medical history of heart disease, high blood pressure, or kidney or liver disease and to report current use of any medicines to determine if these medicines might interact adversely with fludrocortisone acetate (see **Drug Interactions**).

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

The patient’s understanding of his steroid-dependent status and increased dosage requirement under widely variable conditions of stress is vital. Advise the patient to carry medical identification indicating his dependence on steroid medication and, if necessary, instruct him to carry an adequate supply of medication for use in emergencies.

Stress to the patient the importance of regular follow-up visits to check his progress and the need to promptly notify the physician of dizziness, severe or continuing headaches, swelling of feet or lower legs, or unusual weight gain.

Advise the patient to use the medicine only as directed, to take a missed dose as soon as possible, unless it is almost time for the next dose, and not to double the next dose.

Inform the patient to keep this medication and all drugs out of the reach of children.

Laboratory Tests

Patients should be monitored regularly for blood pressure determinations and serum electrolyte determinations (see **WARNINGS**).

Drug Interactions

When administered concurrently, the following drugs may interact with adrenal corticosteroids.

Amphotericin B or potassium-depleting diuretics (benzothiadiazines and related drugs, ethacrynic acid and furosemide)—enhanced hypokalemia. Check serum potassium levels at frequent intervals; use potassium supplements if necessary (see **WARNINGS**).

Digitalis glycosides—enhanced possibility of arrhythmias or digitalis toxicity associated with

hypokalemia. Monitor serum potassium levels; use potassium supplements if necessary.

Oral anticoagulants—decreased prothrombin time response. Monitor prothrombin levels and adjust anticoagulant dosage accordingly.

Antidiabetic drugs (oral agents and insulin)—diminished antidiabetic effect. Monitor for symptoms of hyperglycemia; adjust dosage of antidiabetic drug upward if necessary.

Aspirin—increased ulcerogenic effect; decreased pharmacologic effect of aspirin. Rarely salicylate toxicity may occur in patients who discontinue steroids after concurrent high-dose aspirin therapy. Monitor salicylate levels or the therapeutic effect for which aspirin is given; adjust salicylate dosage accordingly if effect is altered (see **PRECAUTIONS**, **General**).

Barbiturates, phenytoin, or rifampin—increased metabolic clearance of fludrocortisone acetate because of the induction of hepatic enzymes. Observe the patient for possible diminished effect of steroid and increase the steroid dosage accordingly.

Anabolic steroids (particularly C-17 alkylated androgens such as oxymetholone, methandrostenolone, norethandrolone, and similar compounds)—enhanced tendency toward edema. Use caution when giving these drugs together, especially in patients with hepatic or cardiac disease.

Vaccines—neurological complications and lack of antibody response (see **WARNINGS**).

Estrogen—increased levels of corticosteroid-binding globulin, thereby increasing the bound (inactive) fraction; this effect is at least balanced by decreased metabolism of corticosteroids. When estrogen therapy is initiated, a reduction in corticosteroid dosage may be required, and increased amounts may be required when estrogen is terminated.

Drug/Laboratory Test Interactions

Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false-negative results.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate studies have not been performed in animals to determine whether fludrocortisone acetate has carcinogenic or mutagenic activity or whether it affects fertility in males or females.

Pregnancy

Teratogenic Effects: Category C

Adequate animal reproduction studies have not been conducted with fludrocortisone acetate. However, many corticosteroids have been shown to be teratogenic in laboratory animals at low doses. Teratogenicity of these agents in man has not been demonstrated. It is not known whether fludrocortisone acetate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fludrocortisone acetate should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Infants born of mothers who have received substantial doses of fludrocortisone acetate during pregnancy should be carefully observed for signs of hypoadrenalism.

Maternal treatment with corticosteroids should be carefully documented in the infant’s medical records to assist in follow up.

Nursing Mothers

Corticosteroids are found in the breast milk of lactating women receiving systemic therapy with these agents. Caution should be exercised when fludrocortisone acetate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Adverse Reactions

Most adverse reactions are caused by the drug's mineralocorticoid activity (retention of sodium and water) and include hypertension, edema, cardiac enlargement, congestive heart failure, potassium loss, and hypokalemic alkalosis.

When fludrocortisone is used in the small dosages recommended, the glucocorticoid side effects often seen with cortisone and its derivatives are not usually a problem; however the following untoward effects should be kept in mind, particularly when fludrocortisone is used over a prolonged period of time or in conjunction with cortisone or a similar glucocorticoid.

Musculoskeletal—muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, and spontaneous fractures.

Gastrointestinal—peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis.

Dermatologic—impaired wound healing, thin fragile skin, bruising, petechiae and ecchymoses, facial erythema, increased sweating, subcutaneous fat atrophy, purpura, striae, hyperpigmentation of the skin and nails, hirsutism, acneiform eruptions, and hives; reactions to skin tests may be suppressed.

Neurological—convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, and severe mental disturbances.

Endocrine—menstrual irregularities; development of the cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (e.g., trauma, surgery, or illness); decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; and increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic—posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and exophthalmos.

Metabolic—hyperglycemia, glycosuria, and negative nitrogen balance due to protein catabolism.

Allergic Reactions—allergic skin rash, maculopapular rash, and urticaria.

Other adverse reactions that may occur following the administration of a corticosteroid are necrotizing angiitis, thrombophlebitis, aggravation or masking of infections, insomnia, syncopal episodes, and anaphylactoid reactions.

Overdosage

Development of hypertension, edema, hypokalemia, excessive increase in weight, and increase in heart size are signs of overdosage of fludrocortisone acetate. When these are noted, administration of the drug should be discontinued, after which the symptoms will usually subside within several days; subsequent treatment with fludrocortisone acetate should be with a reduced dose. Muscular weakness may develop due to excessive potassium loss and can be treated by administering a potassium supplement. Regular monitoring of blood pressure and serum electrolytes can help to prevent overdosage (see **WARNINGS**).

Dosage and Administration

Dosage depends on the severity of the disease and the response of the patient. Patients should be continually monitored for signs that indicate dosage adjustment is necessary, such as remissions or exacerbations of the disease and stress (surgery, infection, trauma) (see **WARNINGS** and **PRECAUTIONS**, **General**).

Addison's Disease

In Addison's disease, the combination of Fludrocortisone Acetate Tablets with a glucocorticoid such as hydrocortisone or cortisone provides substitution therapy approximating normal adrenal activity with minimal risks of unwanted effects.

The usual dose is 0.1 mg of Fludrocortisone Acetate Tablets daily, although dosage ranging from 0.1 mg three times a week to 0.2 mg daily has been employed. In the event transient hypertension develops as a consequence of therapy, the dose should be reduced to 0.05 mg daily. Fludrocortisone Acetate Tablets are preferably administered in conjunction with cortisone (10 mg to 37.5 mg daily in divided doses) or hydrocortisone (10 mg to 30 mg daily in divided doses).

Salt-Losing Adrenogenital Syndrome

The recommended dosage for treating the salt-losing adrenogenital syndrome is 0.1 mg to 0.2 mg of Fludrocortisone Acetate Tablets daily.

How Supplied

Fludrocortisone Acetate Tablets, USP 0.1 mg are Round, White Tablets, Scored, Debossed "W" on the plain side and "46" on scored side.

Bottles of 30 tablets
Bottles of 100 tablets

Storage

Store at 20-25ºC (68-77ºF) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, NJ 07724

Issued January 2010

Principal Display Panel

Fludrocortisone Acetate Tablets, USP
0.1 mg/30 Tablets
NDC 0143-1246-30

FLUDROCORTISONE ACETATE

fludrocortisone acetate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-1246
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FLUDROCORTISONE ACETATE (UNII: V47IF0PVH4) (FLUDROCORTISONE - UNII:U0476M545B)	FLUDROCORTISONE ACETATE	0.1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CORN STARCH 3-E-DODECENYL SUCCINIC ANHYDRIDE MODIFIED (UNII: QG4MW19XYX)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	W;46
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0143-1246-01	100 in 1 BOTTLE		
2	NDC:0143-1246-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091302	07/22/2011	

Labeler - West-ward Pharmaceutical Corp (001230762)

Establishment

Name	Address	ID/FEI	Business Operations
West-ward Pharmaceutical Corp		001230762	MANUFACTURE

Revised: 7/2011 West-ward Pharmaceutical Corp