

**PILOCARPINE HYDROCHLORIDE OPHTHALMIC- pilocarpine
hydrochloride solution/ drops
Amneal Pharmaceuticals NY LLC**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION 1.25% safely and effectively. See full prescribing information for PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION 1.25%.

**PILOCARPINE HYDROCHLORIDE ophthalmic solution 1.25%, for topical ophthalmic use
Initial U.S. Approval: 1974**

----- **INDICATIONS AND USAGE** -----

Pilocarpine hydrochloride is a cholinergic muscarinic receptor agonist indicated for the treatment of presbyopia in adults. (1)

----- **DOSAGE AND ADMINISTRATION** -----

Instill one drop of pilocarpine hydrochloride ophthalmic solution 1.25% in each eye once daily. (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Ophthalmic solution containing pilocarpine hydrochloride USP, 1.25%. (3)

----- **CONTRAINDICATIONS** -----

Hypersensitivity. (4)

----- **WARNINGS AND PRECAUTIONS** -----

Blurred Vision: Patients should be advised not to drive or operate machinery if vision is not clear (e.g., blurred vision). Exercise caution in night driving and other hazardous activities in poor illumination. (5.1)
Risk of Retinal Detachment: Rare cases of retinal detachment and retinal tear have been reported with miotics, including pilocarpine hydrochloride ophthalmic solution. Individuals with pre-existing retinal disease are at increased risk. Therefore, examination of the retina is advised in all patients prior to initiation of therapy. Patients should be advised to seek immediate medical care with sudden onset of flashing lights, floaters or vision loss. (5.2)
Iritis: Caution is advised in patients with iritis. (5.3)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (> 5%) are headache, conjunctival hyperemia and eye irritation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Pilocarpine hydrochloride ophthalmic solution is indicated for the treatment of presbyopia in adults.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of pilocarpine hydrochloride ophthalmic solution is one drop in each eye once daily.

If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Pilocarpine hydrochloride ophthalmic solution, USP is a clear, colorless, sterile ophthalmic solution containing 1.25% (12.5 mg/mL) of pilocarpine hydrochloride.

4 CONTRAINDICATIONS

Pilocarpine hydrochloride ophthalmic solution is contraindicated in patients with known hypersensitivity to the active ingredient or to any of the excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Blurred Vision

Miotics, including pilocarpine hydrochloride ophthalmic solution, may cause accommodative spasm. Patients should be advised not to drive or operate machinery if vision is not clear (e.g., blurred vision).

In addition, patients may experience temporary dim or dark vision with miotics, including pilocarpine hydrochloride ophthalmic solution. Patients should be advised to exercise caution in night driving and other hazardous activities in poor illumination.

5.2 Risk of Retinal Detachment

Rare cases of retinal detachment and retinal tear have been reported with miotics, including pilocarpine hydrochloride ophthalmic solution.

Individuals with pre-existing retinal disease are at increased risk. Therefore, examination of the retina is advised in all patients prior to the initiation of therapy.

Patients should be advised to seek immediate medical care with sudden onset of flashing lights, floaters or vision loss.

5.3 Iritis

Pilocarpine hydrochloride ophthalmic solution is not recommended to be used when iritis is present because adhesions (synechiae) may form between the iris and the lens.

5.4 Use with Contact Lenses

Contact lens wearers should be advised to remove their lenses prior to the instillation of pilocarpine hydrochloride ophthalmic solution and to wait 10 minutes after dosing before reinserting their contact lenses.

5.5 Potential for Eye Injury or Contamination

To prevent eye injury or contamination, care should be taken to avoid touching the dispensing bottle to the eye or to any other surface.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hypersensitivity [*see Contraindications (4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in practice.

Pilocarpine hydrochloride ophthalmic solution dosed once daily was evaluated in 375 participants with presbyopia in two randomized, double-masked, vehicle-controlled studies (GEMINI 1 and GEMINI 2) of 30 days duration. The most common adverse reactions reported in > 5% of participants were headache and conjunctival hyperemia. Ocular adverse reactions reported in 1% to 5% of participants were blurred vision, eye pain, visual impairment, eye irritation and increased lacrimation.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of pilocarpine hydrochloride ophthalmic solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to pilocarpine hydrochloride ophthalmic solution exposure.

Eye disorders: vitreous detachment, vitreomacular traction, retinal tear, retinal detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of pilocarpine hydrochloride ophthalmic solution administration in pregnant women to inform a drug-associated risk. Oral administration of pilocarpine to pregnant rats throughout organogenesis and lactation did not produce adverse effects at clinically relevant doses.

Data

Human Data

No adequate and well-controlled trials of pilocarpine hydrochloride ophthalmic solution have been conducted in pregnant women. In a retrospective case series of 15 women with glaucoma, 4 patients used ophthalmic pilocarpine either pre-pregnancy, during pregnancy or postpartum. There were no adverse effects observed in patients or in their infants.

Animal Data

In embryofetal development studies, oral administration of pilocarpine to pregnant rats throughout organogenesis produced maternal toxicity, skeletal anomalies and reduction in fetal body weight at 90 mg/kg/day (approximately 485-fold higher than the maximum human ophthalmic dose [MHOD] of 0.015 mg/kg/day, on a mg/m² basis).

In a peri-/postnatal study in rats, oral administration of pilocarpine during late gestation through lactation increased stillbirths at a dose of 36 mg/kg/day (approximately 195-fold higher than the MHOD). Decreased neonatal survival and reduced mean body weight of pups were observed at ≥ 18 mg/kg/day (approximately 100 times the maximum human ophthalmic dose of pilocarpine hydrochloride ophthalmic solution).

8.2 Lactation

Risk Summary

There is no information regarding the presence of pilocarpine in human milk, the effects on the breastfed infants, or the effects on milk production to inform risk of pilocarpine hydrochloride ophthalmic solution to an infant during lactation.

Pilocarpine and/or its metabolites are excreted in the milk of lactating rats. Systemic levels of pilocarpine following topical ocular administration are low [see *Clinical Pharmacology* (12.3)] and it is not known whether measurable levels of pilocarpine would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pilocarpine hydrochloride ophthalmic solution and any potential adverse effects on the breastfed child from pilocarpine hydrochloride ophthalmic solution.

Data

Animal Data

Following a single oral administration of ¹⁴C-pilocarpine to lactating rats, the radioactivity concentrations in milk were similar to those in plasma.

8.4 Pediatric Use

Presbyopia does not occur in the pediatric population.

8.5 Geriatric Use

Clinical studies of pilocarpine hydrochloride ophthalmic solution did not include participants aged 65 and over to determine whether they respond differently from younger participants. Other reported clinical experience with ophthalmic pilocarpine solutions have not identified overall differences in safety between elderly and younger participants.

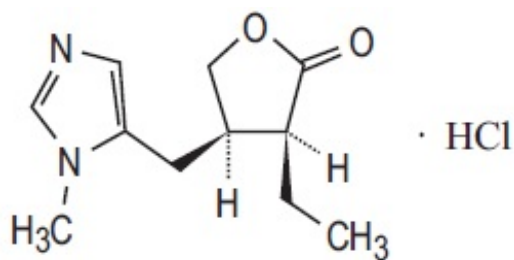
10 OVERDOSAGE

Systemic toxicity following topical ocular administration of pilocarpine is rare, but occasionally patients who are sensitive may develop sweating and gastrointestinal overactivity. Accidental ingestion can produce sweating, salivation, nausea, tremors and slowing of the pulse and a decrease in blood pressure. In moderate overdosage, spontaneous recovery is to be expected and is aided by intravenous fluids to compensate for dehydration. For patients demonstrating severe poisoning, atropine, the pharmacologic antagonist to pilocarpine, should be used.

11 DESCRIPTION

Pilocarpine hydrochloride ophthalmic solution USP, 1.25% is a cholinergic muscarinic receptor agonist prepared as an isotonic, clear, colorless, sterile ophthalmic solution containing 1.25% of pilocarpine hydrochloride, USP. The chemical name for pilocarpine hydrochloride, USP is (3S,4R)-3-ethyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-oxolan-2-

one hydrochloride. Its molecular weight is 244.72 g/mol and its molecular formula is $C_{11}H_{16}N_2O_2 \cdot HCl$. Its structural formula is:



Pilocarpine hydrochloride, USP is a white or almost white, crystalline powder or colorless crystals hygroscopic. It is very soluble in water and freely soluble in alcohol, slightly soluble in chloroform and insoluble in ether.

Each mL of Pilocarpine Hydrochloride Ophthalmic Solution, USP contains:

Active: Pilocarpine hydrochloride USP, 1.25% (12.5 mg) equivalent to 1.06% (10.6 mg) pilocarpine free-base.

Preservative: Benzalkonium chloride, 0.0075%.

Inactives: Boric acid, sodium citrate dihydrate, sodium chloride, water for injection and may also include hydrochloric acid and/or sodium hydroxide for pH adjustment to between 3.5 and 5.5, if necessary.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pilocarpine hydrochloride is a cholinergic muscarinic agonist which activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. Pilocarpine hydrochloride contracts the iris sphincter muscle, constricting the pupil to improve near and intermediate visual acuity while maintaining some pupillary response to light. Pilocarpine hydrochloride also contracts the ciliary muscle and may shift the eye to a more myopic state.

12.3 Pharmacokinetics

Systemic exposure to pilocarpine was evaluated in 22 participants with presbyopia who were administered 1 drop of pilocarpine hydrochloride ophthalmic solution in each eye once daily for 30 days (GEMINI 1). The mean (SD) C_{max} and AUC values from time 0 to last measurable concentration over 10-hour period post-last dose on Day 30 were 1.95 (0.98) ng/mL and 4.14 (2.16) ng·hr/mL, respectively. The median T_{max} value on Day 30 was 0.3 hours post-dose with a range from 0.2 hours to 0.5 hours post-dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Pilocarpine did not induce tumors in mice at any dosage level studied (up to 30 mg/kg/day; approximately 80-times the MHOD). In rats, an oral dose of 18 mg/kg/day (approximately 100 times the MHOD), resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both male and female rats and a statistically significant increase in the incidence of hepatocellular adenomas in female rats.

Mutagenesis

Pilocarpine did not show any potential to cause genetic toxicity 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.

Impairment of Fertility

Pilocarpine oral administration to male and female rats at a dosage of 18 mg/kg/day (100 times the MHOD) 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 males, females or both. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day for 6 months resulted in evidence of impaired spermatogenesis (approximately 55 times the MHOD).

14 CLINICAL STUDIES

The efficacy of pilocarpine hydrochloride ophthalmic solution dosed once daily for the treatment of presbyopia was demonstrated in two 30-Day Phase 3, randomized, double-masked, vehicle-controlled studies, namely GEMINI 1 (NCT03804268) and GEMINI 2 (NCT03857542). A total of 750 participants aged 40 years to 55 years old with presbyopia were randomized (375 to pilocarpine hydrochloride ophthalmic solution group) in two studies and participants were instructed to administer one drop of pilocarpine hydrochloride ophthalmic solution or vehicle once daily in each eye.

In both studies, the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular distance corrected near visual acuity (DCNVA), without losing more than 1 line (5 letters) of corrected distance visual acuity (CDVA) with the same refractive correction was statistically significantly greater in the pilocarpine hydrochloride group compared to the vehicle group at Day 30, Hour 3 (see Table 1).

Table 1: Primary Efficacy Results from GEMINI 1 and GEMINI 2 Studies (Intent-to-Treat Population)

	GEMINI 1			GEMINI 2		
	Pilocarpine Hydrochloride	Vehicle N=160	p-value	Pilocarpine Hydrochloride	Vehicle N=215	p-value

	Ophthalmic Solution N=163			Ophthalmic Solution N=212		
Proportion of participants gaining 3-lines or more in mesopic DCNVA, without losing more than 1 line (5 letters) of CDVA at Day 30, Hour 3	31%	8%	p < 0.01	26%	11%	p < 0.01

Figures 1 and 2 present the proportion of participants who gained 3-lines or more in mesopic DCNVA at Day 30.

Figure 1: Proportion of Participants Achieving 3-Lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 1 (Intent-to-Treat Population)

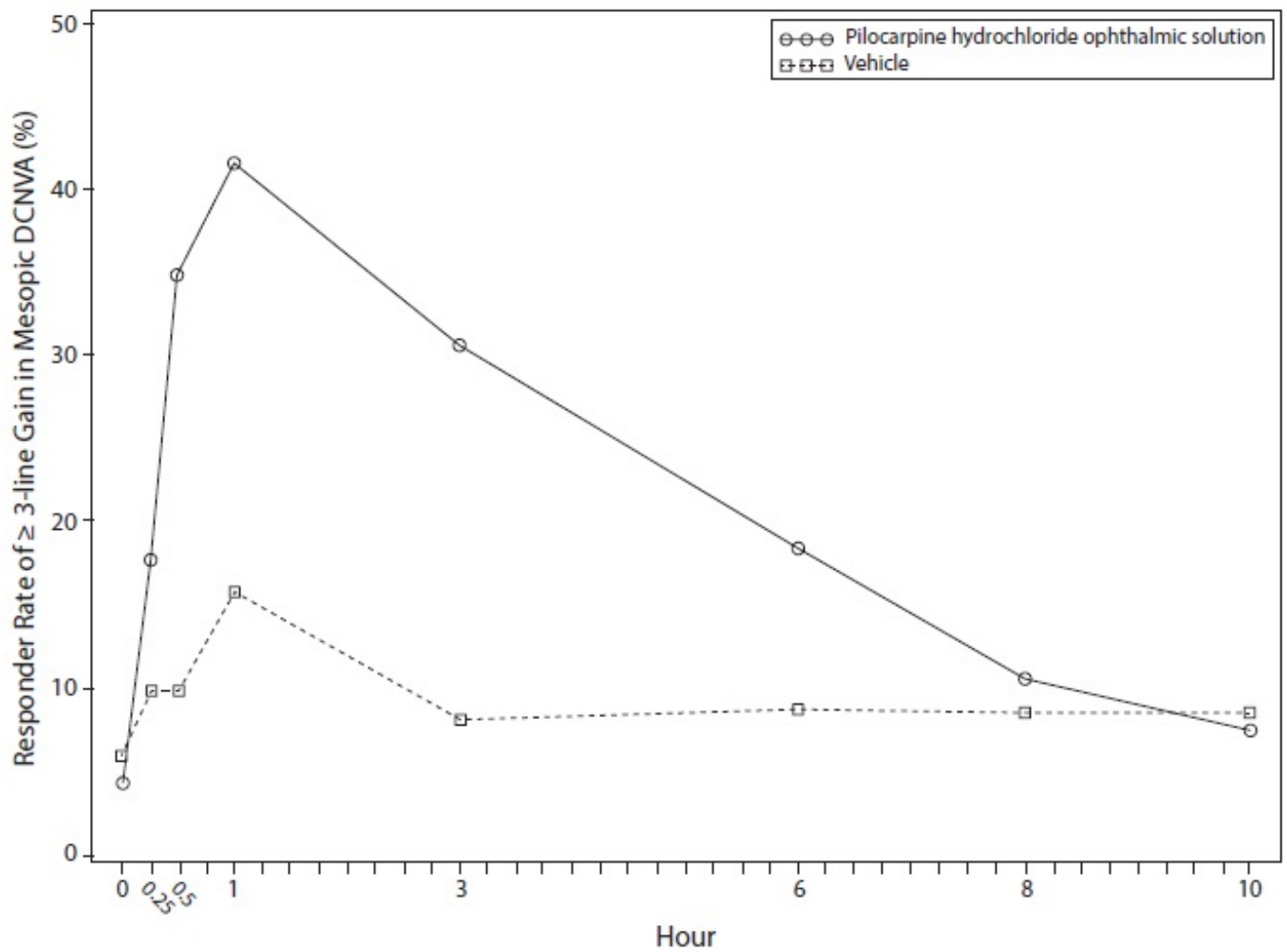
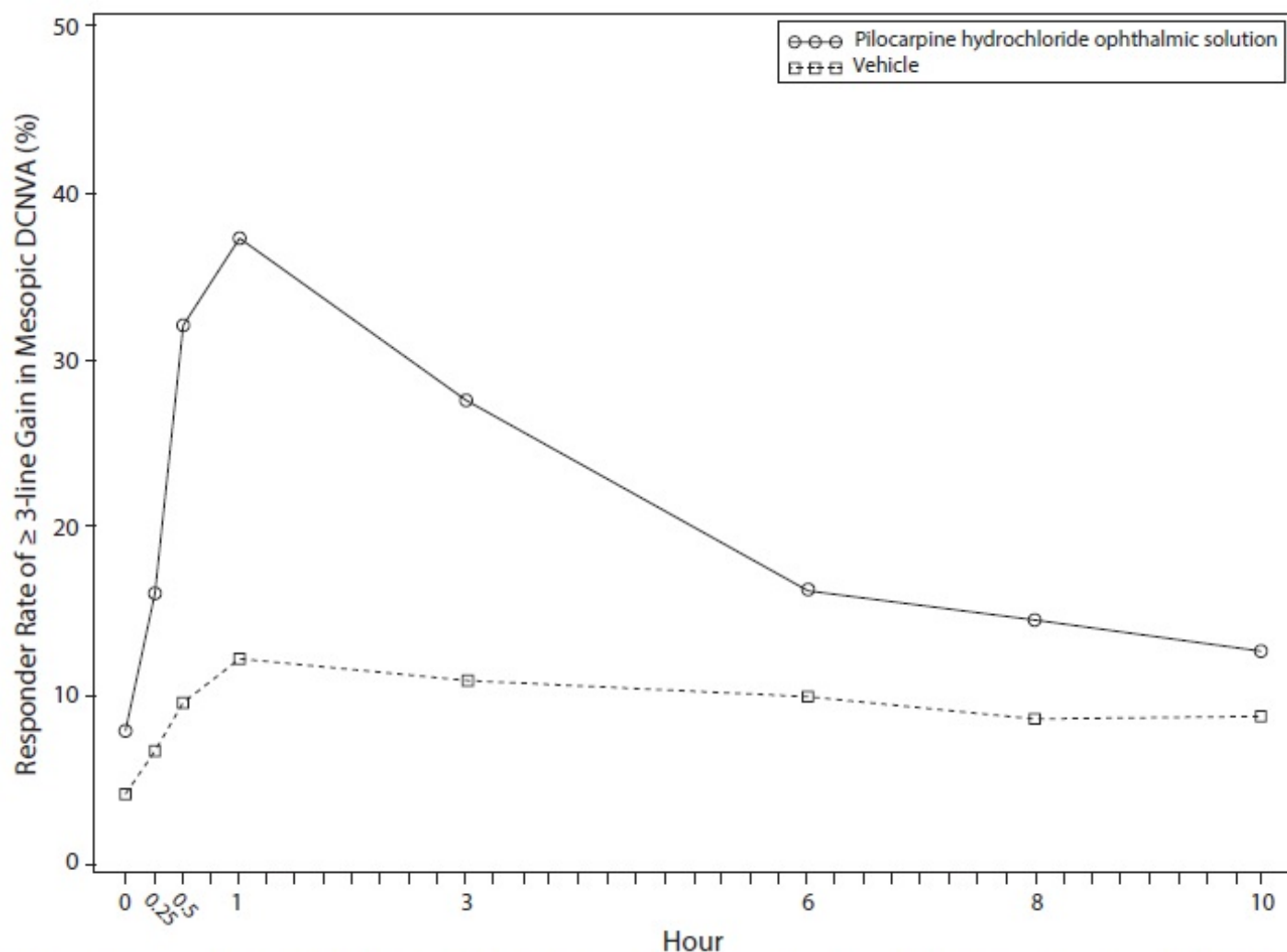


Figure 2: Proportion of Participants Achieving 3-lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 2 (Intent-to-Treat Population)



Timepoint	Hour 0	Hour 0.25	Hour 0.5	Hour 1	Hour 3	Hour 6	Hour 8	Hour 10
Pilocarpine hydrochloride ophthalmic solution (%)	7.8	16.1	32.1	37.3	27.6	16.3	14.5	12.6
Vehicle (%)	4.0	6.6	9.6	12.1	10.8	9.9	8.6	8.7
Difference (95% CI)	3.8 (-0.9, 8.4)	9.4 (3.2, 15.7)	22.5 (14.7, 30.3)	25.2 (17.0, 33.4)	16.7 (9.1, 24.3)	6.5 (-0.1, 13.1)	5.9 (-0.5, 12.2)	3.8 (-2.3, 10.0)

16 HOW SUPPLIED/STORAGE AND HANDLING

Pilocarpine Hydrochloride Ophthalmic Solution USP, **1.25%** is supplied as a sterile, clear, colorless solution filled in low density polyethylene white opaque bottle and low density polyethylene white opaque nozzle with, dark green colored high density polyethylene cap. It is available as follows:

2.5 mL in 5 mL Bottle (Filled to 1/2 Capacity):
2366-2

NDC 60219-

Storage

Store at 15° to 25°C (59° to 77°F). After opening, pilocarpine hydrochloride ophthalmic solution, USP can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Night Driving

Pilocarpine hydrochloride ophthalmic solution may cause temporary dim or dark vision. Advise patients to exercise caution with night driving and when hazardous activities are undertaken in poor illumination [see *Warnings and Precautions* (5.1)].

Accommodative Spasm

Temporary problems when changing focus between near and distant objects may occur. Advise patients not to drive or use machinery if vision is not clear (e.g., blurred vision) [see *Warnings and Precautions* (5.1)].

When to Seek Physician Advice

Advise patients to seek immediate medical care with sudden onset of flashing lights, floaters or vision loss [see *Warnings and Precautions* (5.2)].

Contact Lens Wear

Contact lens should be removed prior to the instillation of pilocarpine hydrochloride ophthalmic solution. Wait 10 minutes after dosing before reinserting contact lenses [see *Warnings and Precautions* (5.4)].

Avoiding Contamination of the Product

Do not touch dropper tip to any surface, as this may contaminate the contents [see *Warnings and Precautions* (5.5)].

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Manufactured by:

Amneal Pharmaceuticals Pvt. Ltd.

Ahmedabad 382213, INDIA

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 05-2025-00

PRINCIPAL DISPLAY PANEL

NDC 60219-2366-2

Pilocarpine Hydrochloride Ophthalmic Solution USP, 1.25% (2.5 mL)

Rx only

Amneal Pharmaceuticals LLC

NDC 60219-2366-2 2.5 mL

**Pilocarpine
Hydrochloride
Ophthalmic
Solution, USP**

1.25%



For Topical Application in the Eye

Sterile Rx only

Recommended Dosage:
See Prescribing Information.

Storage: Store at 15° to
25°C (59° to 77°F).

Note: 2.5 mL in a
5 mL bottle.

Distributed by: **Anneal
Pharmaceuticals LLC**
Bridgewater, NJ 08807

Mfg. Lic. No. G/28/1539

Made in INDIA.

Rev. 05-2025-00



(01) 0 03602 19 23662 2

Unvarnished Area
(6 x 14 mm)

LOT : XXXXXXXX
EXP : YYYY-MM
Unvarnished area for
Batch coding details
to be Printed online
(10 x 14 mm)



PILOCARPINE HYDROCHLORIDE OPHTHALMIC

pilocarpine hydrochloride solution/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:60219-2366
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
PILOCARPINE HYDROCHLORIDE (UNII: 0VW6D218XJ) (PILOCARPINE - UNII:01MI4Q9DI3)			PILOCARPINE HYDROCHLORIDE	12.5 mg in 1 mL
Inactive Ingredients				
Ingredient Name				Strength
BORIC ACID (UNII: R57ZHV85D4)				
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)				
SODIUM CHLORIDE (UNII: 451W47IQ8X)				
WATER (UNII: 059QF0KO0R)				
HYDROCHLORIC ACID (UNII: QTT17582CB)				
SODIUM HYDROXIDE (UNII: 55X04QC32I)				
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60219-2366-2	1 in 1 CARTON	05/01/2025	
1		2.5 mL in 1 BOTTLE, DROPPER; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA		ANDA217733	05/01/2025	

Labeler - Amneal Pharmaceuticals NY LLC (123797875)

Establishment			
Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals Private Limited		860156658	analysis(60219-2366) , manufacture(60219-2366) , pack(60219-2366) , sterilize(60219-2366)

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Amneal Pharmaceuticals NY LLC