

ATROPINE- atropine sulfate solution/ drops Apotex Corp.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ATROPINE SULFATE OPHTHALMIC SOLUTION, safely and effectively. See full prescribing information for ATROPINE SULFATE OPHTHALMIC SOLUTION.

ATROPINE SULFATE Ophthalmic Solution, for topical application to the eye.

Initial U.S. Approval: 1960

INDICATIONS AND USAGE

Atropine is an anti-muscarinic agent indicated for:

- Cycloplegia (1.1)
- Mydriasis (1.2)
- Penalization of the healthy eye in the treatment of amblyopia (1.3)

DOSAGE AND ADMINISTRATION

- In individuals from three (3) months of age or greater, 1 drop topically to the cul-de-sac of the conjunctiva, forty minutes prior to the intended maximal dilation time (2.1)
- In individuals 3 years of age or greater, doses may be repeated up to twice daily as needed. (2.2)

DOSAGE FORMS AND STRENGTHS

1% ophthalmic solution (3)

CONTRAINDICATIONS

Hypersensitivity or allergic reaction to any ingredient in formulation (4.1)

WARNINGS AND PRECAUTIONS

- Photophobia and blurred vision due to pupil unresponsiveness and cycloplegia may last up to 2 weeks. (5.1)
- Risk of blood pressure increase from systemic absorption (5.2)

ADVERSE REACTIONS

Most common adverse reactions that have been reported are eye pain and stinging on administration, blurred vision, photophobia, decreased lacrimation, increased heart rate and blood pressure (6)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

The use of atropine and monoamine oxidase inhibitors (MAOI) is generally not recommended because of the potential to precipitate hypertensive crisis. (7)

USE IN SPECIFIC POPULATIONS

Should only be used in pregnant women if clearly needed (8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2023

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Atropine sulfate ophthalmic solution, 1% is indicated for:

1.1 Cycloplegia

1.2 Mydriasis

1.3 Penalization of the healthy eye in the treatment of amblyopia

2. DOSAGE AND ADMINISTRATION

2.1 In individuals from three (3) months of age or greater, 1 drop topically to the cul-de-sac of the conjunctiva, forty minutes prior to the intended maximal dilation time.

2.2 In individuals 3 years of age or greater, doses may be repeated up to twice daily as needed.

3. DOSAGE FORMS AND STRENGTHS

Atropine sulfate ophthalmic solution, USP 1%: each mL contains 10 mg of atropine sulfate equivalent to 8.3 mg of atropine.

4. CONTRAINDICATIONS

4.1 Hypersensitivity to any Component of this Medication

Atropine sulfate ophthalmic solution should not be used in anyone who has demonstrated a previous hypersensitivity or known allergic reaction to any ingredient of the formulation because it may recur.

5. WARNINGS AND PRECAUTIONS

5.1 Photophobia and Blurred Vision

Photophobia and blurred vision due to pupil unresponsiveness and cycloplegia may last up to 2 weeks.

5.2 Elevation of Blood Pressure

Elevation in blood pressure from systemic absorption has been reported following conjunctival instillation of recommended doses of atropine sulfate ophthalmic solution, 1%.

6. ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Photophobia and Blurred Vision [*see Warnings and Precautions (5.1)*]
- Elevation in Blood Pressure [*see Warnings and Precautions (5.2)*]

The following adverse reactions have been identified following use of atropine sulfate 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 drug exposure.

6.1 Ocular Adverse Reactions

Eye pain and stinging occurs upon instillation of atropine sulfate ophthalmic solution. Other commonly occurring adverse reactions include, blurred vision, photophobia, superficial keratitis and decreased lacrimation. Allergic reactions such as papillary conjunctivitis, contact dermatitis, and lid edema may also occur less commonly.

6.2 Systemic Adverse Reactions

Systemic effects of atropine are related to its anti-muscarinic activity. Systemic adverse events reported include dryness of skin, mouth, and throat from decreased secretions from mucus membranes; restlessness, irritability or delirium from stimulation of the

central nervous system; tachycardia; flushed skin of the face and neck.

7. DRUG INTERACTIONS

7.1 Monoamine oxidase inhibitors (MAOI)

The use of atropine and monoamine oxidase inhibitors (MAOI) is generally not recommended because of the potential to precipitate hypertensive crisis.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of atropine sulfate in pregnant women. Animal development and reproduction studies have not been conducted with atropine sulfate. Since it is not known whether topically administered atropine sulfate can cause fetal harm, atropine sulfate ophthalmic solution, 1% should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Traces of atropine have been found in human milk following administration of atropine solution for injection. Because some systemic absorption occurs from topical administration, caution should be exercised when atropine sulfate ophthalmic solution, 1% is administered to a nursing woman.

8.4 Pediatric Use

Due to the potential for systemic absorption of atropine sulfate ophthalmic solution, the use of atropine sulfate ophthalmic solution, 1% in children under the age of 3 months is not recommended and the use in children under 3 years of age should be limited to no more than one drop per eye per day.

8.5 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger adult patients.

10. OVERDOSAGE

In the event of accidental ingestion or toxic overdosage with atropine sulfate ophthalmic solution supportive care may include a short acting barbiturate or diazepam as needed to control marked excitement and convulsions. Large doses for sedation should be avoided because central depressant action may coincide with the depression occurring late in atropine poisoning. Central stimulants are not recommended.

Physostigmine, given by slow intravenous injection of 1 to 4 mg (0.5 to 1 mg in pediatric populations), rapidly abolishes delirium and coma caused by large doses of atropine. Since physostigmine is rapidly destroyed, the patient may again lapse into coma after

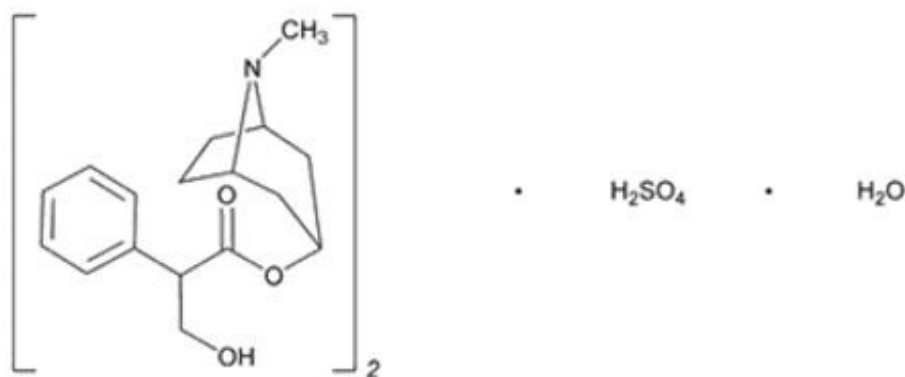
one to two hours, and repeated doses may be required.

Artificial respiration with oxygen may be necessary. Cooling measures may be needed to help to reduce fever, especially in pediatric populations.

The fatal adult dose of atropine is not known. In pediatric populations, 10 mg or less may be fatal.

11. DESCRIPTION

Atropine sulfate ophthalmic solution, USP 1% is a sterile topical anticholinergic for ophthalmic use. The active ingredient is represented by the chemical structure



Chemical Name: Benzeneacetic acid, α -(hydroxymethyl)-, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, endo -(\pm)-, sulfate (2:1) (salt), monohydrate.

Molecular Formula: (C₁₇H₂₃NO₃)₂ • H₂SO₄ • H₂O

Molecular Weight: 694.84 g/mol

Atropine sulfate appears as white or almost white, crystalline powder, or colorless crystals. It is very soluble in water and freely soluble in ethanol (96%).

Atropine sulfate ophthalmic solution, USP 1% is a clear, colorless, slightly viscous solution.

Each mL of Atropine Sulfate Ophthalmic Solution, USP 1% contains: **Active:** atropine sulfate 10 mg equivalent to 8.3 mg of atropine. **Inactives:** benzalkonium chloride 0.1 mg (0.01%), edetate disodium dihydrate, hypromellose (methocel E4M premium), sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, hydrochloric acid and/or sodium hydroxide may be added to adjust pH (3.5 to 6.0), and water for injection USP.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atropine is a reversible antagonist of muscarine-like actions of acetyl-choline and is therefore classified as an antimuscarinic agent. Atropine is relatively selective for

muscarinic receptors. Its potency at nicotinic receptors is much lower, and actions at non-muscarinic receptors are generally undetectable clinically. Atropine does not distinguish among the M1, M2, and M3 subgroups of muscarinic receptors.

The pupillary constrictor muscle depends on muscarinic cholinergic activation. This activation is blocked by topical atropine resulting in unopposed sympathetic dilator activity and mydriasis. Atropine also weakens the contraction of the ciliary muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate such that the eye cannot focus for near vision.

12.2 Pharmacodynamics

The onset of action after administration of atropine sulfate ophthalmic solution, USP 1%, is usually within 40 minutes with maximal effect being reached in about 2 hours. The effect can last for up to 2 weeks in a normal eye.

12.3 Pharmacokinetics

The bioavailability of atropine sulfate ophthalmic solution, 1% was assessed in six healthy subjects, 24 to 29 years of age. Subjects received either 0.3 mg atropine sulfate administered as bolus intravenous injection or 0.3 mg administered as 30 mcL instilled unilaterally in the cul-de-sac of the eye. Plasma l-hyoscyamine concentrations were determined over selected intervals up to eight hours after dose administration.

The mean bioavailability of topically applied atropine was $63.5 \pm 29\%$ (range 19 to 95%) with large inter-individual differences. Mean maximum observed plasma concentration for the ophthalmic solution was 288 ± 73 pg/mL. Maximum concentration was reached in 28 ± 27 min after administration. Terminal half-life of l-hyoscyamine was not affected by route of administration and was calculated to be 3 ± 1.2 hours (intravenous) and 2.5 ± 0.8 hours (topical ophthalmic).

In another placebo-controlled study, the systemic exposure to l-hyoscyamine, and the anti-cholinergic effects of atropine were investigated in eight ocular surgery patients 56 to 66 years of age, following single topical ocular 0.4 mg atropine dose (given as 40 microliters of atropine sulfate ophthalmic solution, 1%). The mean (\pm standard deviation (SD)) C_{max} of l-hyoscyamine in these patients was 860 ± 402 pg/mL, achieved within 8 minutes of eyedrop instillation.

Following intravenous administration, the mean (\pm SD) elimination half-life ($t_{1/2}$) of atropine was reported to be longer in pediatric subjects under 2 years (6.9 ± 3.3 hours) and in geriatric patients 65 to 75 years (10 ± 7.3 hours), compared to in children over 2 years (2.5 ± 1.2 hours) and in adults 16 to 58 years (3 ± 0.9 hours). (see 8.4 Pediatric Use).

Atropine is destroyed by enzymatic hydrolysis, particularly in the liver; from 13 to 50% is excreted unchanged in the urine. Traces are found in various secretions, including milk. The major metabolites of atropine are noratropine, atropin-n-oxide, tropine, and tropic acid. Atropine readily crosses the placental barrier and enters the fetal circulation but is not found in amniotic fluid.

Atropine binds poorly (about 44%) to plasma protein, mainly to α -1 acid glycoprotein; age has no effect on the serum protein binding of atropine. Atropine binding to α -1 acid glycoprotein was concentration dependent (2 to 20 mcg/mL) and nonlinear *in vitro* and *in vivo*. There is no gender effect on the pharmacokinetics of

atropine administered by injection.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Atropine sulfate was negative in the Salmonella/microsome mutagenicity test. Studies to evaluate carcinogenicity and impairment of fertility have not been conducted.

14. CLINICAL STUDIES

Topical administration of atropine sulfate ophthalmic solution, 1% results in cycloplegia and mydriasis which has been demonstrated in several controlled clinical studies in adults and pediatric patients. Maximal mydriasis usually occurs in about 40 minutes and maximal cycloplegia is usually achieved in about 60 to 90 minutes after single administration. Full recovery usually occurs in approximately one week but may last a couple of weeks.

16. HOW SUPPLIED/STORAGE AND HANDLING

Atropine sulfate ophthalmic solution, USP 1% is supplied in a plastic dropper bottle with a red cap in the following sizes:

NDC 60505-6226-0 2 mL bottle

NDC 60505-6226-1 5 mL bottle

NDC 60505-6226-2 15 mL bottle

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

17. PATIENT COUNSELING INFORMATION

Advise patients not to touch the dropper tip to any surface as this may contaminate the solution.

Advise patients that drops will sting upon instillation and advise patients that they will experience sensitivity to light and blurred vision which may last for a couple of weeks.

Manufactured By	Manufactured For
Apotex Inc.	Apotex Corp.
Toronto, Ontario	Weston, Florida
Canada M9L 1T9	USA 33326

Revised: August 2021

Rev. 3

Principal Display Panel Text for Container Label:

NDC 60505-6226-0

Atropine Sulfate

Ophthalmic

Solution, USP

1%

FOR TOPICAL

APPLICATION TO THE EYE

Sterile

Rx only

2 mL

2 mL NDC 60505-6226-0

Atropine Sulfate
Ophthalmic Solution, USP

1%

FOR TOPICAL APPLICATION
TO THE EYE
Rx Only

Sterile
APOTEX CORP.

Each mL contains: **Active:** Atropine Sulfate 10 mg (1%), the amount of atropine in 10 mg of atropine sulfate is 8.3 mg. **Preservative:** Benzalkonium Chloride 0.1 mg (0.01%). **Storage:** Store at 20°C to 25°C (68°F to 77°F). Keep tightly closed. **WARNING - KEEP OUT OF THE REACH OF CHILDREN.**

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9
Manufactured for: Apotex Corp. Weston, Florida 33326

413838

Principal Display Panel Text for Container Label:

NDC 60505-6226-1

Atropine Sulfate

Ophthalmic

Solution, USP

1%

FOR TOPICAL

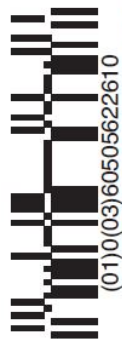
APPLICATION TO THE EYE

Sterile

Rx only

5 mL

5 mL NDC 60505-6226-1



Atropine Sulfate
Ophthalmic Solution, USP

1%

FOR TOPICAL APPLICATION
TO THE EYE
Rx Only

Sterile

APOTEX CORP.

Each mL contains: **Active:** Atropine Sulfate 10 mg (1%), the amount of atropine in 10 mg of atropine sulfate is 8.3 mg. **Preservative:** Benzalkonium Chloride 0.1 mg (0.01%). **Storage:** Store at 20°C to 25°C (68°F to 77°F). Keep tightly closed. **WARNING – KEEP OUT OF THE REACH OF CHILDREN.**

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9
Manufactured for: Apotex Corp. Weston, Florida 33326

413836

Principal Display Panel Text for Container Label:

NDC 60505-6226-2

Atropine Sulfate

Ophthalmic

Solution, USP

1%

FOR TOPICAL


APPLICATION TO THE EYE

Sterile

Rx only

15 mL

15 mL NDC 60505-6226-2



Atropine Sulfate
Ophthalmic Solution, USP

1%

FOR TOPICAL APPLICATION
TO THE EYE
Rx Only

Sterile

APOTEX CORP.

Each mL contains: **Active:** Atropine Sulfate 10 mg (1%), the amount of atropine in 10 mg of atropine sulfate is 8.3 mg. **Preservative:** Benzalkonium Chloride 0.1 mg (0.01%). **Storage:** Store at 20°C to 25°C (68°F to 77°F). Keep tightly closed. **WARNING – KEEP OUT OF THE REACH OF CHILDREN.**

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9
Manufactured for: Apotex Corp. Weston, Florida 33326

413840

Principal Display Panel Text for Carton Label:

60505-6226-0

Atropine

Sulfate

Ophthalmic

Solution, USP

1%

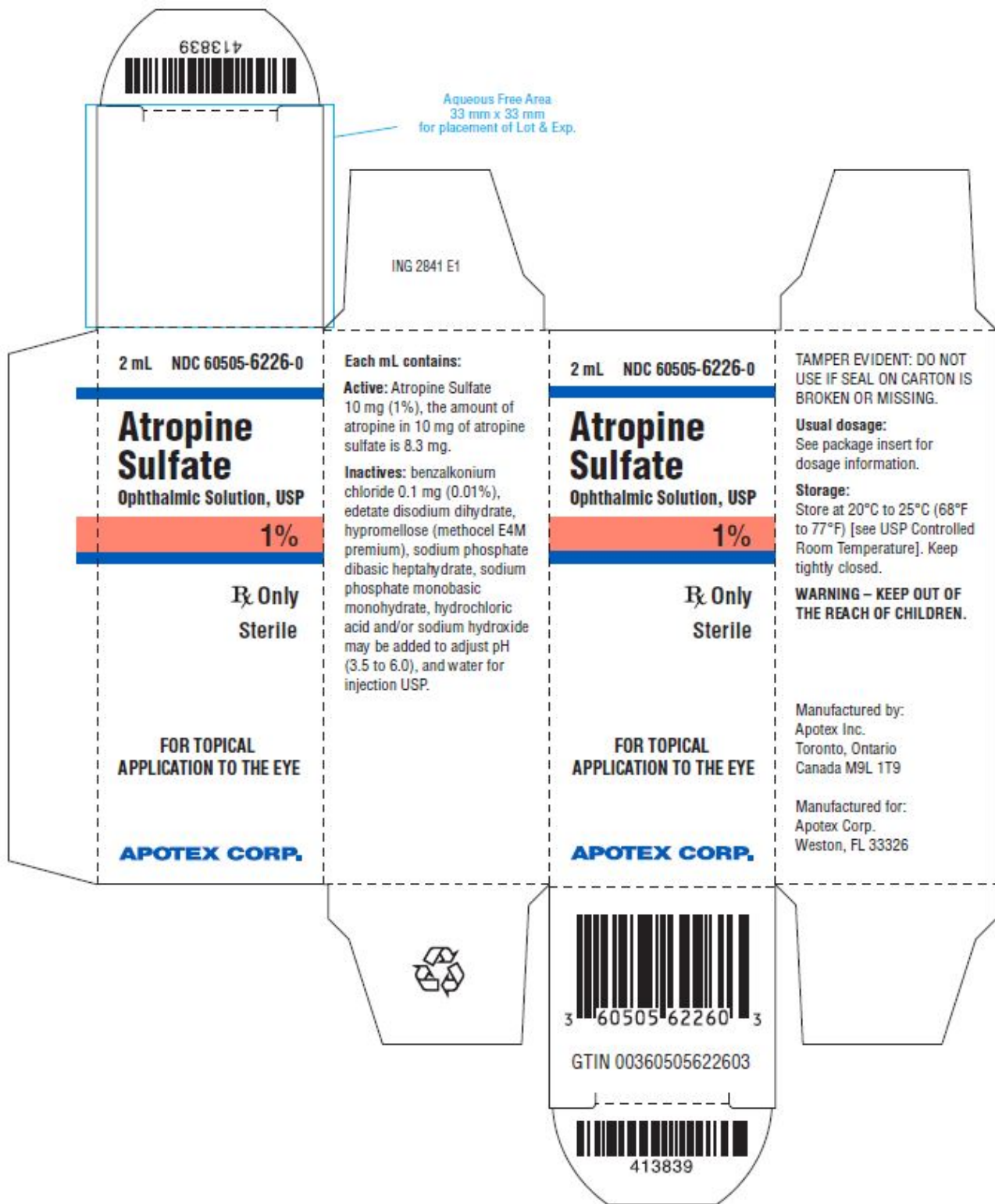
FOR TOPICAL APPLICATION

TO THE EYE

Sterile

2 mL

Rx only



Principal Display Panel Text for Carton Label:

60505-6226-1

Atropine

Sulfate

Ophthalmic

Solution, USP

1%

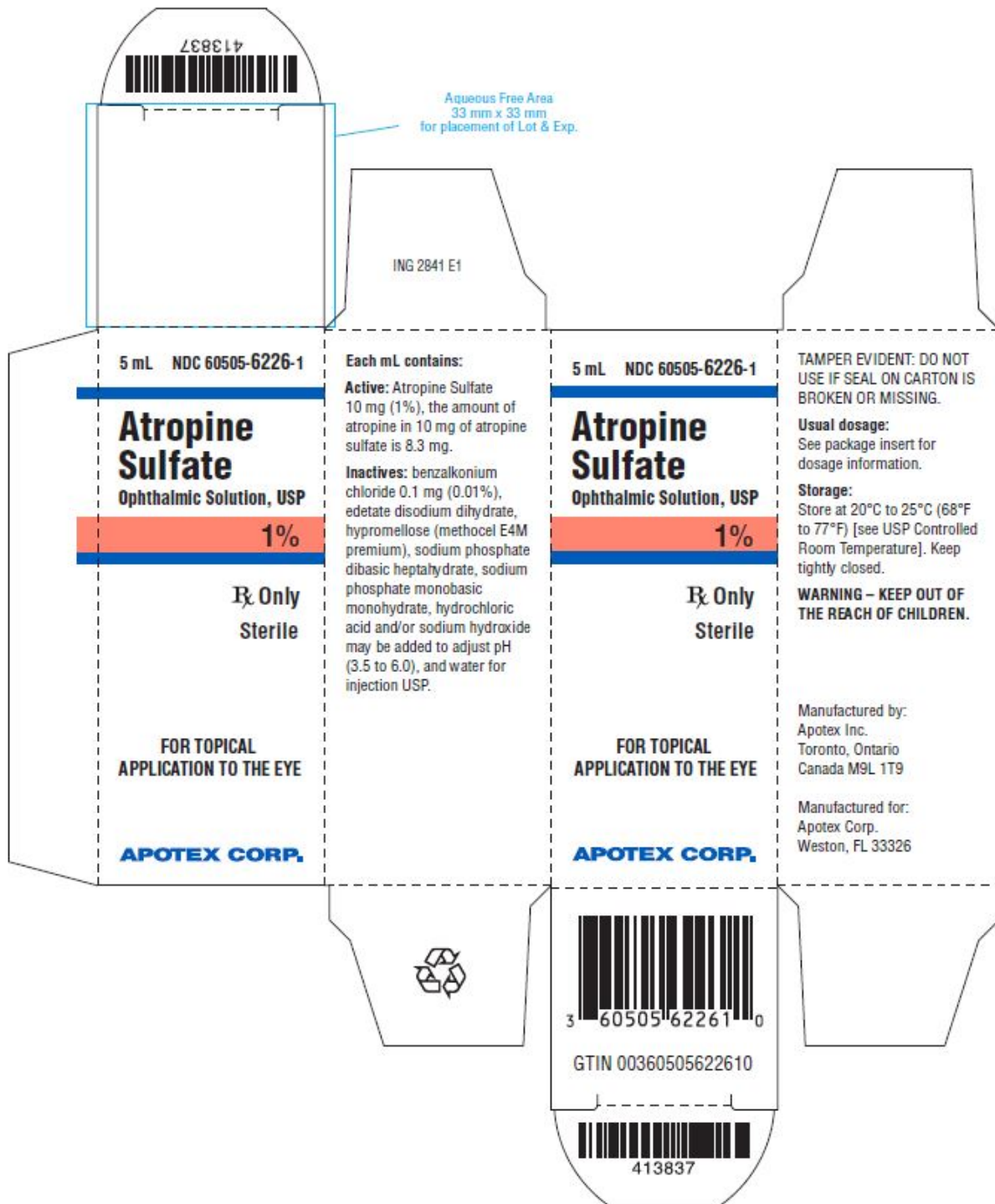
FOR TOPICAL APPLICATION

TO THE EYE

Sterile

5 mL

Rx only



Principal Display Panel Text for Carton Label:

60505-6226-2

Atropine

Sulfate

Ophthalmic

Solution, USP

1%

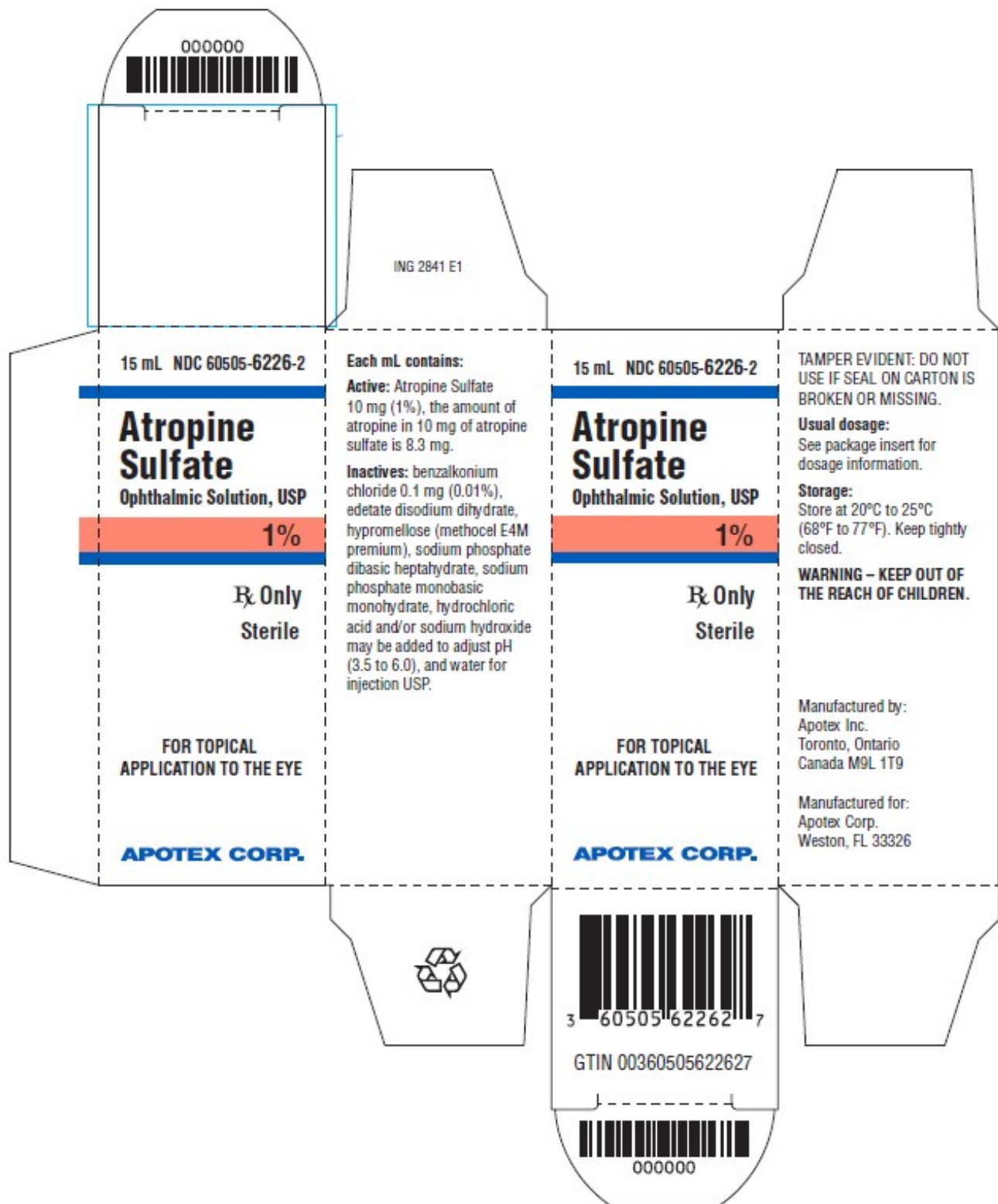
FOR TOPICAL APPLICATION

TO THE EYE

Sterile

15 mL

Rx only



ATROPINE

atropine sulfate solution/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:60505-6226
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATROPINE SULFATE (UNII: 03J5ZE7KA5) (Atropine - UNII:7C0697DR9I)	ATROPINE SULFATE	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
HYPROMELLOSE 2910 (4000 MPA.S) (UNII: RN3152OP35)	
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM (UNII: 3980JIH2SW)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60505-6226-0	1 in 1 CARTON	11/26/2021	
1		2 mL in 1 BOTTLE, DROPPER; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:60505-6226-1	1 in 1 CARTON	11/26/2021	
2		5 mL in 1 BOTTLE, DROPPER; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
3	NDC:60505-6226-2	1 in 1 CARTON	02/07/2022	
3		15 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	ANDA215624	11/26/2021	

Labeler - Apotex Corp. (845263701)**Registrant** - Apotex Inc. (209429182)**Establishment**

Name	Address	ID/FEI	Business Operations
Apotex Inc.		255092496	analysis(60505-6226) , manufacture(60505-6226)

