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Atropine Sulfate Ophthalmic
Solution, USP 1%



ASOON

Rev. 08/14

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Atropine Sulfate Ophthalmic Solution, USP 1% safely and effectively. See full prescribing information for Atropine Sulfate Ophthalmic Solution, USP 1%.

Atropine Sulfate Ophthalmic Solution, USP 1% 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 individual 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)
- In individuals 3 years of age or greater, doses may be repeated up to twice daily as needed. (2)

DOSAGE FORMS AND STRENGTHS
1% ophthalmic solution (3)

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE
Atropine Sulfate Ophthalmic Solution, USP 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

- 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.
- 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
Elevations in blood pressure from systemic absorption has been reported following conjunctival instillation of recommended doses of atropine sulfate ophthalmic solution, USP 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 mucous 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.

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 Akorn, Inc. at 1-800-932-5676 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: 08/2014

7 DRUG INTERACTIONS
7.1 Monoamine oxidase inhibitors (MAOI)

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, USP 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, USP 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, USP 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.

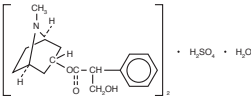
10. OVERDOSAGE
In the event of accidental ingestion or toxic overdose with atropine sulfate ophthalmic solution, supportive care may include a short acting barbiturate or diazepam as needed to control marked excitement and convulsions. Large doses for sedation should be avoided because central depressant 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: Benzenesacetic acid, α-(hydroxymethyl)-, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, *sn*o- (-)-, sulfate (2:1) (salt), monohydrate.

Molecular Formula: (C₁₇H₂₇NO₃)₂ • H₂SO₄ • H₂O

Molecular Weight: 694.83 g/mol

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%), dibasic sodium phosphate, edetate disodium, hypromellose (2910), monobasic sodium phosphate, 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, USP 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 µl 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 ± 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, USP 1%). The mean (± 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 (± 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 (10.0 ± 7.3 hours), compared to in children over 2 years (2.5 ± 1.2 hours) and in adults 16 to 58 years (3.0 ± 0.9 hours). (See 6.4 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 alpha-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, USP 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 17478-215-02	2 mL fill in 6cc bottle
NDC 17478-215-05	5 mL fill in 6cc bottle
NDC 17478-215-15	15 mL fill in 15cc bottle

Storage: Store at 20° to 25°C (68° to 77°F). 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.

 **AKORN**
Manufactured by: **Akorn, Inc.**,
Lake Forest, IL 60045

AS00N Rev. 08/14



www.archive.org
415.561.6767
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Internet Archive
300 Funston Avenue
San Francisco, CA 94118

AFFIDAVIT OF DUNCAN HALL

1. I am a Records Request Processor at the Internet Archive, located in San Francisco, California. I make this declaration of my own personal knowledge.
2. The Internet Archive is a website that provides access to a digital library of Internet sites and other cultural artifacts in digital form. Like a paper library, we provide free access to researchers, historians, scholars, and the general public. The Internet Archive has partnered with and receives support from various institutions, including the Library of Congress.
3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to browse more than 450 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a display of available dates. The visitor may select one of those dates, and begin browsing an archived version of the Web. Links on archived files in the Wayback Machine point to other archived files (whether HTML pages or other file types), if any are found for the URL indicated by a given link. For instance, the Wayback Machine is designed such that when a visitor clicks on a hyperlink on an archived page that points to another URL, the visitor will be served the archived file found for the hyperlink's URL with the closest available date to the initial file containing the hyperlink.
4. The archived data made viewable and browseable by the Wayback Machine is obtained by use of web archiving software that automatically stores copies of files available via the Internet, each file preserved as it existed at a particular point in time.
5. The Internet Archive assigns a URL on its site to the archived files in the format `http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL]` aka an "extended URL". Thus, the extended URL `http://web.archive.org/web/19970126045828/http://www.archive.org/` would be the URL for the record of the Internet Archive home page HTML file (`http://www.archive.org/`) archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28). A web browser may be set such that a printout from it will display the URL of a web page in the printout's footer. The date indicated by an extended URL applies to a preserved instance of a file for a given URL, but not necessarily to any other files linked therein. Thus, in the case of a page constituted by a primary HTML file and other separate files (e.g., files with images, audio, multimedia, design elements, or other embedded content) linked within that primary HTML file, the primary HTML file and the other files will each have their own respective extended URLs and may not have been archived on the same dates.



6. Attached hereto as Exhibit B are true and accurate electronic copies of the Internet Archive's records of the archived files for the URLs and the dates specified in the table below for the individual electronic file folder within which each file is saved:

Folder Name	URL
01	https://web.archive.org/web/20150317035537/http://akorn.com/documents/catalog/package_inserts/17478-215-15.pdf

7. I declare under penalty of perjury that the foregoing is true and correct.

DATE: 12/30/2020

Duncan D Hall

Duncan Hall

JURAT

State/Commonwealth of TEXAS)
)
☐ City ☒ County of Harris)

On 12/30/2020, before me, Ikome Chefor,
Date Notary Name

the foregoing instrument was subscribed and sworn (or affirmed) before me by:

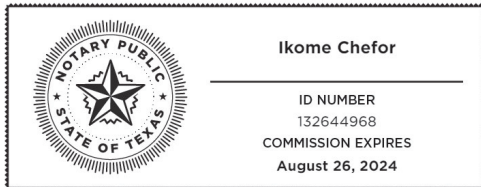
Duncan D Hall
Name of Affiant(s)

☐ Personally known to me -- OR --

☐ Proved to me on the basis of the oath of _____ -- OR --
Name of Credible Witness

☒ Proved to me on the basis of satisfactory evidence: driver license
Type of ID Presented

WITNESS my hand and official seal.



Notary Public Signature: _____

Notary Name: Ikome Chefor

Notary Commission Number: 132644968

Notary Commission Expires: 08/26/2024

Notarized online using audio-video communication

DESCRIPTION OF ATTACHED DOCUMENT

Title or Type of Document: affidavit

Document Date: _____

Number of Pages (including notarial certificate): 3