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RESEARCH**

APPLICATION NUMBER:

206289Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 206289
Supplement #	N/A
Related IND	pIND 118218
Applicant Name	Akorn Inc.
Application Type	505(b)(2)
Date of Submission	10/22/2013
Receipt Date	10/30/2014
PDUFA Goal Date	04/30/2014 (priority)
Proprietary Name / Established (USAN) Name	None atropine sulfate ophthalmic solution
Dosage Forms / Strength	solution /eye drops 1%
Preservative	benzalkonium chloride, 0.01% (0.1 mg/mL)
Route of Administration	Topical
Therapeutic Class	Anti-muscarinic
Indication(s)	Cycloplegia Mydriasis Amblyopia
Dosage Regimen	see labeling
How Supplied	in plastic dropper bottle with red cap in the following sizes: 2mL fill in 6cc bottle; 5 mL fill in 6cc bottle; 15mL fill in 15cc bottle
Action/Recommended	<i>approval</i>

Pharmacokinetic parameters of atropine (measured as l-hyoscyamine) following topical ocular administration of 1% atropine sulfate ophthalmic solution

Ref.	Study Objective	Study Design	Treatment (Dose/Dosage Form/Route)	Subjects (No.(M/F), Type, Age (Mean, Range))	Pharmacokinetic Parameters (Mean ± SD) for l-hyoscyamine)					
					Cmax (pg/mL)	Tmax (min)	AUC ₍₀₋₄₎ (h.ng/mL)	AUC _(0-inf) (h.ng/mL)	t _{1/2} (h)	CL (mL/min/kg)
Kaila et al. (1999)	Determine absolute bioavailability of topical ocular atropine	Open label, randomized, crossover, with 2-week washout period	0.3 mg, single dose, IV solution	6 (1M/5F), Healthy, 24-29 y	NA	NA	NA	1.79 ± 0.64	2.97 ± 1.22	2.3E-5 ± 6.5E-6
			0.3 mg, single dose, ophthalmic solution		288.3 ± 72.91	27.67 ± 26.85	NA	1.02 ± 0.33	2.45 ± 0.76	4E-5 ± 3.1E-5
Lahdes, et al. (1988)	Determine pharmacokinetics of ophthalmic administration	Open label, randomized, parallel, vs. placebo	0.4 mg, ophthalmic solution	8 (7M/1F), ocular surgery patients, 56-66 y	860 ± 402	8	0.72 ± 0.40 ^a	NA	NA	NA

^aconverted to h*ng/mL from AUC of 43.25 ± 24.1 min*ng/mL
 Source: Clinical Pharmacology Review

Ocular Pharmacodynamics (PD):

With 1% atropine sulfate ophthalmic solution, full mydriasis is achievable with 1 drop; multiple eyedrops are needed to achieve full cycloplegia. Full recovery from these effects could take up to 18 days.

Mydriasis

Based on the study conducted Wolf and Hodge (1946)⁹ in healthy subjects 16 to 37 years old, 1 drop of 1% atropine sulfate ophthalmic solution into the eye produced a maximum pupil diameter of 8.3 mm (2.5-fold greater than normal size) within 40 minutes of eye drop instillation. Recovery started at 6 hours after instillation of the eye drop, and it took up to 12 days for the pupil diameter to fully return to its normal size.

Cycloplegia

Based on the study conducted by Marron (1940)¹⁰ in subjects 15 to 40 years old, 1 drop of 1% atropine sulfate ophthalmic solution instilled in the eye three times daily for 3 days with an additional 1 drop on the morning of the day of the ocular examination produced a residual accommodation (RA) of 1.9 D (17% of baseline); maximum effect was observed after the 4th of 10 drops. The average patient was able to read newsprint by the third day after the last instillation, and it took up to 18 days for the range of accommodation to fully return to normal. (In this study, the maximum extent of pupil dilation or mydriasis was achieved after the first drop and did not increase further with the instillation of additional eyedrops.)

The clinical pharmacology reviewer concludes that: Based on literature data, 65% (on average) and up to 95% (on an individual basis) of the administered topical ocular dose of atropine is absorbed. One drop (actual drop volume ~ 40 mcL) of 1% atropine sulfate ophthalmic solution contains 0.4 mg atropine sulfate. No dosage adjustment is needed for

⁹ Wolf AV, Hodge HC. Effects of atropine sulfate, methylatropine nitrate (metropine) and homatropine hydrobromide on adult human eyes. *Arch Ophthal* 1946; 36: 293-301.

¹⁰ Marron J. Cycloplegia and mydriasis by use of atropine, scopolamine, and homatropine-paradrine. *Arch Ophthalmol* 1940; 23: 340-50.

patients with dark irides for adequate pupil dilation (mydriasis) and complete and uniform cycloplegia. No dose adjustment is needed based on gender or race. No dosage adjustment is needed for elderly patients, patients with renal impairment or patients with hepatic impairment; these patients should be monitored for systemic adverse reactions such as change in blood pressure and heart rate given they may have impairment in elimination of atropine. No dosage adjustment is needed for pediatric patients ≥ 4 years in age. The clinical pharmacology reviewer notes that the medical literature prior to 1951 reports four pediatric deaths in patients between 10 months and 3 years in age who received atropine 1%; the total estimated doses were between 1.6 to 18 mg given as over 1 to 2 days. No pediatric deaths associated with atropine 1% are reported since the 1950's. Therefore patients 3 months to 3 years should receive only single doses (0.4 mg) and children under the age of 3 months should not receive atropine eyedrops.

Labeling will reflect that: 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 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 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 μ l 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 ophthalmic solution, 1%). The mean (\pm standard deviation (SD)) C_{max} of 1-hyoscyamine in these patients was 860 ± 402 pg/mL, achieved within 8 minutes of eye drop 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 (10.0 ± 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).

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 (2-20 μ g/mL) and nonlinear in vitro and in vivo. There is no gender effect on the pharmacokinetics of atropine administered by injection.

Comment:

I concur with the conclusions reached by the clinical pharmacology reviewers to recommend approval. Labeling revisions to this section have been completed. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

For details, see the Clinical and Statistical reviews. A brief summary is provided below.

The applicant identified several hundred publications based on their literature search and selected six publications to support efficacy of atropine for their 505(b)(2) application. The medical officer identified and reviewed fifty-seven studies published between 1931 and 2013 evaluating atropine in the proposed indications. Eight representative studies were reviewed and summarized in the primary reviews. These studies evaluated atropine, including the atropine 1% solution. The studies included subjects from 2 months to 92 years in age. The Chia¹¹ study of (b) (4) did not evaluate 1% atropine and was conducted over 2 years and did not provide 5 year data considered necessary from the ophthalmology perspective. The remaining seven trials are summarized below.

¹¹ Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the treatment of childhood (b) (4): safety and efficacy of 0.5%, 0.1%, and 0.01% doses. *Ophthalmology* 2012;119(2):347-54

Mydriasis and Cycloplegia

Six selected representative studies in support of the indications of mydriasis and cycloplegia are listed in the table below:

Mydriasis and/or cycloplegia results for studies of atropine 1% ophthalmic solution
Mydriasis (dilation) is measured by pupil diameter and cycloplegia is measured by accommodation (A) or residual accommodation (RA)

Study	Dilation Results for Atropine 1%	Dilation Results for Control or other arm	Cycloplegia Results for Atropine 1%	Cycloplegia Results for Control or other arm
Barbee 1957	Mean baseline ~4mm Mean posttrt ~6.5 mm No difference among races and eye colors. (Fig 1)	All 7 other agents had mean dilation greater than 6 mm. One agent, scopolamine, had a mean value>atropine	Change in pupil size (A) close to zero (Fig 2 bottom) A after treatment<0.1 mm	All other active agents had values >atropine (thereby the other agents are less effective)
Ebri 2007	100% had dilation ≥ 6mm	For cyclopentolate, 53% had dilation ≥ 6mm For cyclopentolate +0.5%Tropicamide, 94% had dilation ≥ 6mm	100% had RA 0-0.5 D Mean RA 0.04 D Sign. Lower RA than other agents p<0.0001	For cyclopentolate, 54% had RA 0-0.5 D Mean 0.63 D For cyclopentolate +0.5%Tropicamide, 71% had RA 0-0.5 D Mean 0.36 D
Marron 1940	Average full dilation of 7.9 mm By 40 minutes	For scopolamine, average full dilation of 8 mm For Homatropine, average full dilation of 8 mm	Average minimum A of 1.9 D (ratio RA ~0.16 from Fig 3) Full effect after 4 drops/fell within 30'	For scopolamine, minimum A of 1.6D (ratio RA ~0.18) For Homatropine, minimum A of 1.6D (ratio RA ~0.18)
Wolf 1946	Average full dilation of 8.3 mm	For Methylatropine, average full dilation of 7.7 mm For Homatropine, average full dilation of 5.9 mm	Mean RA of 0.21 (ratio)	For Methylatropine, Mean RA of 0.29 (ratio) For Homatropine, Mean RA of 0.55 (ratio)
Kawamoto 1997	NA	NA	Mean refraction <6yrs +3.55 D >7yrs +2.60 D	For Cyclopentolate, Mean refraction <6yrs +2.89 D >7yrs +1.83 D
Stolovitch 1992	NA	NA	Mean refraction ~3D	NA

Source: statistical review
 D=dipters

As summarized in the statistical review, six publications provided results for cycloplegia and/or mydriasis. These six studies were 1 day to 7 days in length and provide statistical data that support the indications of mydriasis and cycloplegia. The subject populations for the six studies together include children (ages 5 months to 18 years) and adults (ages 19-60 years). Two publications (Kawamoto, 1997 and Stolovitch, 1992)¹² provided refraction data and no

¹² Kawamoto K, Hayasaka S. Cycloplegic refractions in Japanese children: a comparison of atropine and cyclopentolate. *Ophthalmologica* 1997; 211:57-60.
 Stolovitch C, Loewenstein A, Nemmet P, Lazar M. Atropine cycloplegia: how many instillations does one need? *J Pediatr Ophthalmol Strabismus* 1992; 29:175-176.

results for accommodation; the clinical reviewer noted refraction data are not sufficient for demonstrating cycloplegia.

Four of the publications (Barbee, 1957; Ebri, 2007; Marron, 1940; Wolf, 1946)¹³ provided results to support indications for cycloplegia and mydriasis. In these studies, 229 children and adults were given atropine 1% and showed that mean dilation due to atropine treatment ranged from 6.5 to 8.3 mm, with the majority of subjects having values above 6 mm. Some other drugs (scopolamine and homatropine) had slightly larger values for dilation as seen in one study by Marron. In this trial, administration of atropine 1% resulted in clinically significant mydriasis within 40 minutes and clinically significant cycloplegia for at least 8 hours. The Barbee study showed no differences between the races and eye colors studied with all groups showing mean dilation values greater than 6 mm. The Wolf study showed clinically significant pupil dilation within 40 minutes, lasting for at least 6 hours and clinically significant cycloplegia within 5 hours, lasting for at least one day.

One study of the four studies (Ebri) was a randomized, controlled study that provided statistical evidence of the effect of atropine 1% compared to cyclopentolate and tropicamide plus cyclopentolate. Atropine was superior to cyclopentolate and cyclopentolate/tropicamide at increasing dilation and reducing residual accommodation ($p < 0.03$).

The clinical reviews summarize additional clinical studies that report clinically significant pupil dilation (> 6 mm) and clinically important cycloplegia.

Both clinical and statistical reviewers concluded that the mydriasis effect and the cycloplegia effect of atropine 1% was consistent across a broad subject population with the majority of subjects showing dilation of 6 mm or more and minimal accommodation from light stimulation. These effects were generally comparable or better than what was observed for a variety of controls.

Amblyopia

Atropine 1% for the treatment of amblyopia was studied by the Pediatric Eye Disease Group¹⁴ in a randomized, blinded study of 193 children at 39 centers. Children aged 7 to 12 years (mean of 9 years) were randomized to weekend atropine 1% ($n=95$) or patching of the sound eye ($n=98$). Stratifying was based on visual acuity in the amblyopic eye and study center. In the sound eye, patching was to be done 2 hours a day or atropine 1% was to be given on both weekend days. Treatment was to be continued for 17 weeks; if vision improved but the amblyopia had not resolved, treatment continued and children were tested every 8 weeks.

¹³ Barbee, R. F., Smith W. O. Jr. A comparative study of mydriatic and cycloplegic agents; in human subjects without eye disease. *Am J Ophthalmol* 1957; 44(5 Pt 1):617-22.

Ebri A, Kuper H, Wedner S. Cost-effectiveness of cycloplegic agents: results of a randomized controlled trial in Nigerian children. *Invest Ophthalmol Vis Sci* 2007; 48(3):1025-31.

Marron J. Cycloplegia and mydriasis by use of atropine, scopolamine, and homatropine-paradrine. *Arch Ophthalmol* 1940; 23: 340-50.

Wolf AV, Hodge HC. Effects of atropine sulfate, methylatropine nitrate (metropine) and homatropine hydrobromide on adult human eyes. *Arch Ophthalmol* 1946; 36: 293-301.

¹⁴ Pediatric Eye Disease Investigator Group. Patching vs. atropine to treat amblyopia in children aged 7 to 12 years. *Arch Ophthalmol* 2008; 126(12):1634-1642.

Follow-up visits were planned for Week 5 and Week 17. If acuity was not increased by 5 letters or more by the Week 5 visit, patching was increased to 4 hours daily or atropine was given daily. About 90% of randomized subjects completed the study. About 1/3 of subjects had their treatment regimen increased in each arm. By Week 17, 54% of atropine-treated subjects and 58% of patched subjects were still taking the randomized regimen.

The primary outcome in this study is visual acuity at Week 17 (range Week 13 to Week 26) in the amblyopic eye measured in letters using the Early Treatment Diabetic Retinopathy Study test. The tester was blinded to treatment. A score of 85 letters corresponds approximately to 20/20 vision.

The authors used an analysis of covariance model with baseline acuity as a covariate to analyze the treatment difference for acuity at Week 17; their stated goal was to show equivalence between the two treatments where equivalence was defined by a 95% confidence interval that excluded a difference of 5 letters or greater in favor of either treatment.

The visual acuity result for mean number of letters measured at Week 17 was 71 letters for patching and 69 letters for atropine, the difference +1.2 letters and 95% CI (-0.7, +3.1). This difference is not significant based on the authors' criterion of excluding 5 letters from the confidence interval on the difference. When using cutoffs to assess acuity (better than 20/25 and 15 or more letters), a higher percentage (7-8%) of patched subjects showed improvement than atropine subjects, however the difference was not statistically significant.

	Atropine 1%	Patching	Patching-Atropine ¹ (1-sided 95% CI)
Baseline Acuity (letters) Amblyopic eye mean (SD) Sound eye mean (SD) Intereye difference	n=95 62 (7) 86 (3) 24 (7)	n=98 62 (6) 86 (4) 23.5 (7)	
Week 17 Visual acuity	n=88	n=84	
Mean letters at Week 17	69 (9)	71 (9)	+1.2 (-0.7, +3.1)
Mean change from baseline Wk17	+7.6 (7.5)	+8.6 (7.8)	
N (%) Better than 20/25	15 (17%)	20 (24%)	+7% (-3%, +17%)
N (%) ≥ 15 letters	15 (17%)	21 (25%)	+8% (-2%, +18%)

The reviewers concluded this study, along with the other clinical information, supported the indication of treatment of amblyopia by penalizing the healthy eye.

The Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products¹⁵ discusses the use of published literature to support NDA approval. When published trials are the sole basis for approval, features that make the published data informative include:

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

¹⁵ <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>

- b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
- c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
- d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
- e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

The above guidance further notes that there have been approvals based primarily or exclusively on published reports. Examples cited include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

With the effort by the agency and the Office of Compliance to bring unapproved marketed products to the agency for regulatory review as NDAs, several products have successfully submitted NDAs which were subsequently approved. Examples of ophthalmic solutions that changed from unapproved to approved status based on the submission of a 505(b)(2) application, relying on published clinical trials include epinephrine and phenylephrine. As per the regulations, 21 CFR §320.22 (b)(2), in this and other applications the applicant requested a waiver of bioequivalence studies, since ophthalmic solutions and systemic injection products are considered self-evidently bioequivalent, therefore further bioequivalence testing was not needed.

Other examples of products based on published literature included quinine approved for the treatment of malaria; for this oral product, pharmacokinetic studies showed the product used in several clinical trials was bioequivalent to the proposed US product manufactured by Mutual. Colchicine was another unapproved product which received approval for NDA 22-352 for the treatment of FMF (granted orphan designation), on July 29, 2009; NDA 22-351 for the treatment of acute gout flares on July 30, 2009; and NDA 22-353 for the treatment of chronic gout on October 16, 2009.

Therefore, based on the available regulations and guidances, there is sufficient published literature regarding the mechanism of action, the clinical pharmacology and the safety and efficacy of atropine sulfate ophthalmic solution 1% to support approval of the indications for mydriasis, cycloplegia and treatment of amblyopia.

Labeling will reflect that: 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.

Comment:

I concur there is sufficient data to support indications for mydriasis, cycloplegia and for the treatment of amblyopia, by penalizing the normal eye.

8. Safety

For further details, the Clinical Reviews should be consulted. A brief summary is provided below.

As noted above, atropine has been known for centuries and used for many years; as a result, there is extensive information on adverse reactions associated with atropine. These reactions include elevated blood pressure, ventricular fibrillation, supraventricular or ventricular tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, dry mouth and potentially extreme confusion, dissociative hallucinations and excitation especially amongst the elderly. These latter effects are because atropine is able to cross the blood–brain barrier. Because of the hallucinogenic properties, some have used the drug recreationally, though this is potentially dangerous and often unpleasant.¹⁶

Atropine is incapacitating at doses of 10 to 20 mg per person. In overdoses, atropine is poisonous. Its LD50 is estimated to be 453 mg per person (per oral). The antidote to atropine is physostigmine or pilocarpine.

Regarding the symptoms with overdose, Akorn cites the quote: The adverse effects of atropine may be summarized by the saying: ‘as hot as a hare, blind as a bat, dry as a bone, red as a beetroot, and mad as a hatter’. Patients are ‘blind’ owing to the induced cycloplegia, ‘dry’ and ‘hot’ due to the inhibition of the sweat and salivary glands (one of the first signs of atropine poisoning is a dry mouth), ‘red’ because of peripheral vasodilation (produced in an attempt to lose heat and to overcome the lack of function of the sweat glands) and ‘mad’ owing to effects on the central nervous system (CNS).

One eyedrop of atropine contains 0.4 mg atropine sulfate, and the bioavailability of topically administered ophthalmic solution is about 63%. Therefore the resulting systemic exposure following topical atropine is much lower than following the doses associated with incapacitation and LD50 doses noted above.

The clinical reviewer notes that: Studies have been conducted to evaluate the effect of atropine on the eyes for over 160 years. Studies range from evaluations of a few patients to studies of over 1500 patients. For example, RM Ingram reported on refractions of 1648 children aged 11 to 13 months in which atropine 1% was used for cycloplegia.¹⁷

¹⁶ <http://en.wikipedia.org/wiki/Atropine>

¹⁷ Ingram RM. Refraction of 1-year-old children after atropine cycloplegia. *Br J Ophthalmol* 1979;63:343-7.

The published literature includes reviews of the adverse events of topical atropine as well as individual case reports. Mydriasis and cycloplegia studies often used one to three day regimens of administration. Studies of the treatment of amblyopia and (b) (4) used daily administrations for periods of months (amblyopia) (b) (4)

Eye pain and stinging occurs upon instillation of atropine 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.

The following are the most commonly reported and clinically significant reported adverse reactions. With the exception of the allergic reactions, all are a result of the known and expected pharmacologic action:

- Allergic reactions including contact dermatitis usually confined to the lids and conjunctiva characterized by itching, redness, swelling and discharge.
- Photophobia due to the increase in pupil size.
- Decreased tearing due to inhibition of the lacrimal gland.
- Dryness of the skin, mouth and throat due to decreased secretion from the mucous membranes.
- Restlessness, irritability or delirium due to stimulation of the central nervous system. Most are thought to be due to atropine intoxication and often associated with pre-existing mental health issues.
- Tachycardia. Low dose atropine will initially cause a slowing of the heart rate, but increased dosing can lead to tachycardia.
- Flushed skin of face and neck is an expected pharmacologic anticholinergic reaction.

The use of atropine with monoamine oxidase inhibitors can potentially precipitate a hypertensive crisis; therefore this use is generally not recommended.

In the event of over dosage with atropine sulfate ophthalmic solution, 1%, supportive care may include a short acting barbiturate or diazepam; artificial respiration with oxygen, cooling measures to help to reduce fever. The fatal adult dose of atropine is not known.

Comment:

I concur with the conclusions and recommendations for approval of the application by the clinical reviewers. The labeling has been revised and includes safety information for atropine available from the published literature.

9. Advisory Committee Meeting

Atropine has been marketed in ophthalmic and systemic formulations for years. Akorn has marketed their atropine ophthalmic product since 1995. The application did not identify scientific issues for presentation and discussion at the Advisory Committee meeting.

10. Pediatrics

The published studies included pediatric patients. Labeling states that due to the potential for systemic absorption of atropine, 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 (b) (4) under 3 years of age should be limited to no more than one drop per eye. In pediatric populations, 10 mg or less may be fatal. Physostigmine, given by slow intravenous injection of 1 to 4 mg (0.5 to 1 mg in pediatric populations), abolishes delirium and coma caused by large doses of atropine. Artificial respiration with oxygen and cooling measures to help to reduce fever may be needed.

11. Other Relevant Regulatory Issues

11.1 Office of Compliance Facility Inspections

Manufacturing facilities for the DS and DP were found acceptable June 26, 2014, as documented in EES.

11.2 Office of Scientific Investigation (OSI) Audits

The clinical trials to support this application are from the published literature; there was no source documentation for these trials.

11.3 Debarment Certification

Akorn, Inc. certified that Akorn has not and will not use in any capacity the services of any person who has been debarred under section 306 of the Generic Drug Enforcement Act of 1992 with this application.

11.4 Financial Disclosure

These studies were conducted before requirements to document financial disclosure, and are published studies. No financial information was provided. A financial disclosure form has been completed by the medical officer.

11.5 Other Regulatory Issues

This is a 505(b)(2) application and the 505(b)(2) committee has cleared this application for approval.

There are currently other atropine ophthalmic products being marketed without FDA approved new drug applications; the Office of Compliance will determine the appropriate enforcement actions regarding the unapproved products.

The Office of Executive Programs has been asked to assist in preparing an Information Advisory (IA) regarding the upcoming approval of a previously marketed unapproved product. The IA includes a brief summary of the product, the indications, and the basis for approval of this 505(b)(2) application.

12. Labeling

- No proprietary name was submitted for review.
- Physician labeling (PLR) has been finalized and input from the reviewers and consultants was discussed and incorporated as warranted, and differences in labeling recommendations are addressed in the CDTL review.
- Carton and immediate container labels have been finalized after input from reviewers and consultants was discussed and changes incorporated as warranted
- Patient labeling/Medication guide – these are not proposed for the current product

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 206289, Atropine Sulfate Ophthalmic Solution, USP 1% will be approved for the indications of mydriasis, cycloplegia and treatment of amblyopia by penalizing the healthy eye. All disciplines recommend approval and manufacturing facilities are “acceptable.” Labeling has been finalized.

- Risk Benefit Assessment

Mydriasis (dilation of the pupil) and cycloplegia (temporary paralysis of the accommodation reflex) are induced medically for various diagnostic and treatment reasons in the area of ophthalmology. Amblyopia is a condition where one eye inadequately processes visual signal transmission to the brain, and the brain ignores or ‘turns off’ the signal from the ‘lazy eye.’

There are several products available that can achieve mydriasis and cycloplegia: Currently FDA approved products phenylephrine, tropicamide and cyclopentolate have a treatment duration up to 12 hours. Atropine can achieve mydriasis and cycloplegia for 72 hours or greater. When these actions are necessary for greater than 72 hours either for diagnostic or therapeutic action, there are no pharmacologic alternatives. When maximal cycloplegia is required, there are no therapeutic alternatives.

Because atropine degrades slowly, typically wearing off in 7 to 14 days, it is generally used as a therapeutic mydriatic, whereas tropicamide (a shorter-acting cholinergic antagonist) or phenylephrine (an α -adrenergic agonist) is used as an aid to ophthalmic examination. Atropine induces mydriasis by blocking contraction of the circular pupillary sphincter muscle, which is normally stimulated by acetylcholine release, thereby allowing the radial pupillary dilator muscle to contract and dilate the pupil. Atropine induces cycloplegia by paralyzing the ciliary muscles, whose action inhibits accommodation to allow accurate refraction in children, helps to relieve pain associated with iridocyclitis, and treats ciliary block glaucoma.

Atropine is a naturally occurring tropane alkaloid

(b) (4)

These plants have been known since antiquity. Akorn

reported identifying about two thousand non-clinical reports and hundreds of clinical reports in the published literature, and noted that extensive information is also included in medical textbooks.

The current 505(b)(2) submission is supported by published non-clinical and clinical studies; Akorn also refers to the agency's finding of safety and effectiveness on atropine sulfate injection, NDA 21146 by Hospira. The primary reviewers examined the publications submitted and selected representative publications for review; their findings are documented in their reviews.

The efficacy of atropine is summarized in the clinical and statistical reviews, and shows that topical administration of atropine sulfate ophthalmic solution, 1% results in maximal mydriasis in about 40 minutes and maximal cycloplegia is usually achieved in about 60 to 90 minutes after single administration of an eye drop. Full recovery usually occurs in approximately one week, but may last a couple of weeks. In patients with amblyopia, clinical results showed that the treatment effect of atropine was not significantly different from patching of the healthy eye.

Because of atropine's long history, adverse reactions associated with various doses, including overdoses are known. There are reports of pediatric deaths before the 1950s when young children received total doses ranging from 1.6 to 4 mg. Therefore dosing is not recommended in infants below 3 months and children 3 months to 3 years should receive only a single eyedrop.

The pharmacologic and toxic effect of atropine is related to doses; therefore the dosing regimen is limited to older children (who receive one drop) and to older patients who may receive two doses per day. There is no need to adjust these doses based on race, gender, age, iris color, renal or hepatic impairment.

Systemic absorption of atropine can result in various adverse reactions including increased heart rate, elevated blood pressure, and inhibition of salivation and sweat gland secretions. Pupil dilation is the intended pharmacologic action of atropine.

Overall, the benefit outweighs the risks of atropine when used as labeled and the labeling provides sufficient information for the safe and effective use of the product.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

RENATA ALBRECHT
07/18/2014