Summary of Product Characteristics

TROPIN 0.01%

1. Name of the medicinal product

TROPIN 0.01%

2. Qualitative and quantitative composition

Each 1 mL contains Atropine sulfate 0.1 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Eye drops

Clear, colorless sterile ophthalmic solution

4. Clinical particulars

4.1 Therapeutic indications [1.1]

Tropin 0.01% is indicated as a treatment to slow the progression of myopia in children aged from 4 to 14 years. Atropine treatment may be initiated in children when myopia progresses ≥-1.0 D per year.

4.2 Posology and method of administration [1.2]

Treatment should be supervised by an eyecare professional.

Instill one drop into the eye as required for treatment. To minimise the risk of systemic absorption, gentle pressure should be applied to the tear duct for one minute after application.

Tropin 0.01% eye drops should be administered as one drop to each eye at night. The maximum benefit of treatment may not be achieved with less than a 2 year continued administration period.

The duration of administration should be based on regular clinical assessment. The maximum duration of treatment in the clinical studies was 5 years. There is very little data in support of treatment beyond the age of 14 years.

Each container is for single use and should be discarded after administration of the dose (See Section 6.5 Nature and contents of container).

4.3 Contraindications [1.3]

Tropin 0.01% eye drops are contraindicated in the presence of angle closure glaucoma or where angle closure glaucoma is suspected. If used in glaucoma susceptible patients, an estimation of the depth of the angle of the anterior chamber should be performed prior to the initiation of therapy.

Hypersensitivity to any of the ingredients of Tropin 0.01% eye drops.

4.4 Special warnings and precautions for use [1.4]

Risk benefit should be considered when the following medical problems exist:

Keratoconus

Atropine may produce fixed dilated pupils.

Synechiae

Atropine may increase the risk of adherence of the iris to lens.

Use in children

Atropine sulfate monohydrate should not be used in children who have previously had severe systemic reaction to atropine. An increased susceptibility to atropine has been reported in children with Down's syndrome, spastic paralysis, or brain damage; therefore atropine should be used with great caution in these patients. No difference in myopia progression was observed in children with light and dark-coloured eyes when treated with atropine 0.01% eye drops. Limited clinical evidence is available for the long-term safety of atropine 0.01% eye drops in children and adolescents. It is recommended that regular eye health clinical reviews are conducted if long term treatment is planned, including the monitoring of anterior segment development, IOP, retinal health and myopia progression.

Careful monitoring of anterior segment development should be considered in clinical application of topical atropine for prolonged periods in very young children.

Tropin 0.01% eye drops should not be used in children less than 4 years of age.

Photophobia

If children experience photophobia or glare associated with atropine use, they may be offered polychromatic glasses or encouraged to wear sunglasses. In a clinical study, photophobia was resolved in 72% of the children reporting this effect by using photochromic lenses or sunglasses (see Section 4.8 Undesirable effects).

Poor visual acuity

If children experience poor visual acuity associated with atropine use, they may be prescribed progressive glasses. In a clinical study, poor near vision acuity was improved in 96% of children by the use of multifocal lenses (see Section 4.8 Undesirable effects).

Rebound Myopia upon Discontinuation

Discontinuation of the atropine 0.01% eye drops may lead to a rebound in myopia. In a clinical study, the rates of myopia progression after a 12 month washout for children administered atropine 0.01% eye drops for 2 years was -0.28 ± 0.33 D (see Section 4.8 Undesirable effects).

Use in the elderly

Tropin 0.01% eye drops are not indicated for use in the elderly.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicinal products and other forms of interaction [1.5]

Anticholinergics: If significant systemic absorption of ophthalmic atropine occurs, concurrent use of other anticholinergics or medications with anticholinergic activity may result in potentiated anticholinergic effects.

Antiglaucoma agents: (cholinergic, long acting, ophthalmic). Concurrent use with atropine may antagonise the anti-glaucoma and miotic actions of ophthalmic long acting cholinergic anti-glaucoma agents such as echothiophate. Concurrent use with atropine may also antagonise the anti-accommodative convergence effects of these medications when they are used for the treatment of strabismus. Although no studies are currently available evaluating low dose atropine eye drops in children with elevated IOP, there are some data

to suggest that the use of low dose atropine drops may reduce the risk of glaucoma in myopic children.

Antimyasthenics, potassium citrate, potassium supplements: If significant systemic absorption of ophthalmic atropine occurs, concurrent use may increase the chance of toxicity and/or side effects of these systemic medications because of the anticholinergic induced slowing of gastrointestinal motility.

Carbachol, physostigmine or pilocarpine: Concurrent use with atropine may interfere with the antiglaucoma action of carbachol, physostigmine or pilocarpine. Also, concurrent use may counteract the mydriatic effect of atropine; this counteraction may be used to therapeutic advantage.

CNS depression-producing medications: If significant absorption of systemic atropine occurs, concurrent use of medications having CNS effects, such as antiemetic agents, phenothiazines, or barbiturates, may result in opisthotonos, convulsions, coma, and extrapyramidal symptoms.

4.6 Fertility, pregnancy, and lactation [1.6]

Effects on fertility

No data regarding effects on female fertility are available. Impairment of male fertility has been observed in rats treated with atropine at doses far higher than provided by Tropin therapy (≥62.5 mg/kg/day orally). This was mediated pharmacologically through inhibition of the contractile function of the vas deferens and seminal vesicle in emission; sperm production and motility were unaffected in treated rats.

Use in pregnancy

Pregnancy Category A

Atropine sulfate monohydrate may be systemically absorbed after ocular administration, however significant effects on the fetus have not been reported.

Use in lactation

Systemically absorbed atropine sulfate monohydrate is distributed into breast milk in very small amounts. It may cause adverse effects, such as rapid pulse, fever, or dry skin, in nursing infants of mothers using ophthalmic atropine.

4.7 Effects on ability to drive and use machines [1.7]

While the reported incidence of poor visual acuity associated with the use of 0.01% atropine eye drops in clinical trials was very low, the possible effect on the ability to drive or use machinery should be evaluated, particularly at the commencement of treatment.

4.8 Undesirable effects [1.8]

The following adverse reactions have been reported in association with atropine eyes drops:

Ophthalmic

Blurred vision, local irritation, follicular conjunctivitis, vascular congestion, oedema, exudate, contact dermatitis, eczematous dermatitis.

In clinical trials evaluating the safety of 0.01% atropine eye drops when administered to myopic children treated for up to 2 years, the most common (≥1% and <10%) reported adverse events were photophobia, blurred vision, poor visual acuity and allergy.

Systemic

Systemic atropine toxicity may be manifest as flushing and dryness of the skin, blurred vision, rapid and irregular pulse, fever, abdominal distension in infants, mental aberration and loss of neuromuscular coordination. Severe systemic reactions to atropine are characterised by hypotension with progressive respiratory depression. Higher concentrations of ophthalmic atropine have been associated with cardiac arrhythmias (e.g. atrial fibrillation). The reports occurred in older patients (aged > 75 years) or young children (6 to 10 years). In all cases the patients where using concentrations of atropine eye drops 1% or greater.

Adverse events associated with 0.01% to 1% atropine eye drops

In a meta-analysis by Gong 2017 of adverse events associated with atropine eye drop treatment of myopia in children, the overall incidence of adverse events reported in 2425 patients treated with concentrations ranging from 0.01% to 1% was relatively small (n=308). The most common events were photophobia (25%), poor near visual acuity (7.5%) and allergy (2.9%). The remaining events occurred in less than 1% of subjects. These events increased with increasing concentrations of atropine eye drops. The incidence of photophobia was statistically significant, but highly variable and only moderately correlated with the dose of atropine ($r = 0.56$; $p = 0.03$). The incidence of poor visual acuity with 0.01% drops was 2.3%.

Yam 2018 found that at the 2 week visit the percentage of participants reporting photophobia was 5.5% and 12.6% respectively in those allocated to 0.01% atropine drops and placebo, respectively. This difference was significant ($p< 0.001$). At the 12 month assessment point the percentages had declined to 2.1% for atropine and 4.3% of placebo treated subjects. Change in accommodation amplitude (D) demonstrated a concentration dependent effect ($p< 0.001$), however the change observed in the 0.01% group (-0.26 ± 3.04 D) was no different from the mean change seen with placebo (-0.32 ± 2.91 D; $p = 0.89$). The change in pupil size also demonstrated a concentration dependent effect for both photopic and mesopic measurements, however the change remained stable throughout the trial period.

Other adverse events reported in clinical studies include local irritation, headache and fatigue.

Case reports of tachycardia, atrial fibrillation, cardiac rhythm disturbances, psychosis, confusional state, hallucinations, decrease in consciousness, exacerbation of seizures and bilateral pigment dispersion syndrome, in association with atropine eye drops have been recorded. In all cases the patients were using concentrations of atropine eye drops 1% or greater.

Long-term ocular toxicity of 0.01% to 1% atropine eye drops

The potential for longer term ocular toxicity associated with atropine treatment in myopia, in concentrations from 0.01% to 1%, has been evaluated in several clinical studies.

Luu 2005 and Chia 2013 found that atropine 1%, 0.5%, 0.1% or 0.01% eye drops when used for the treatment of myopia over 2 years, caused no significant retinal dysfunction.

Chua 2006 observed no optic disc, lenticular or macular changes in children treated with 1% atropine eye drops for 2 years. Similarly, Yen 1989 noted no ocular side effects associated with atropine 1% eye drop treatment in children treated for one year.

Wu 2012 found no association between either the cumulative dose or duration of atropine treatment and intraocular pressure (IOP) in children treated with 0.1 to 1% atropine drops for a mean 20.5 months. Chan 2017 studied children using atropine 0.25% drops for up to 70 months and observed no change in IOP, peripapillary RNFL thickness, areas of optic disc, cup or rim thickness or up to disc ratios.

Weng 2017 measured IOP using rebound tonometer in 44 myopic children under 0.15%, 0.3%, or 0.5% atropine treatment. The average IOP of the right eye by rebound tonometer was 17.4 ± 3 mmHg (range: 11–24 mmHg), and 17.1 ± 3 mmHg (range: 12– 22 mmHg) by applanation tonometry.

4.9 Overdose [1.9]

No cases of overdose associated with the use Tropin 0.01% eye drops have been reported.

Following the administered a single dose of 0.3 mg atropine sulfate by ocular instillation as a 1% solution to healthy volunteers, the mean maximum plasma concentration of the active isomer of atropine was between one third and one half of the concentration associated with cardiovascular effects.

Signs of overdosage are similar to those described as systemic effects (see Section 4.8 Undesirable effects). Treatment is symptomatic and supportive.

For systemic effects, 0.2 to 1 mg (0.2 mg in children) physostigmine should be administered intravenously, as a dilution containing 1 mg in 5 mL of normal saline. The

solution should be injected over a period of not less than 2 minutes. Dosage may be repeated every 5 minutes up to a total dose of 2 mg in children and 6 mg in adults in each 30 minute period. Physostigmine is contraindicated in hypertensive reactions.

ECG monitoring is recommended during physostigmine administration.

Excitement may be controlled by diazepam or a short acting barbiturate.

It is recommended that 1 mg of atropine be available for immediate injection if the physostigmine causes bradycardia, convulsion, or bronchoconstriction.

Supportive therapy may require oxygen and assisted respiration; cool water baths for fever, especially in children; and catheterisation for urinary retention. In infants and small children, the body surface should be kept moist.

5. Pharmacological properties

5.1 Pharmacodynamic properties [1.10]

Mechanism of action

Atropine is a non-selective muscarinic receptor antagonist. It acts in the eye to block the action of acetylcholine, relaxing the cholinergically innervated sphincter muscle of the iris. This results in dilation of the pupil (mydriasis). The cholinergic stimulation of the accommodative ciliary muscle of the lens is also blocked. This results in paralysis of accommodation (cycloplegia).

The exact mode of action of atropine attributed to the suppression of the progression of myopia has not been fully elucidated. Muscarinic receptors are widely distributed in ocular tissues, with roles in ocular growth and development, as well as accommodation, recognised. Preclinical studies suggest that atropine acts via binding to the muscarinic receptors located on scleral fibroblasts and possibly in the retina, primarily the M1, M3 and M4 subtypes. This results in changes in the activity of cell signalling proteins and enzymes such as MEK-ERK-MAPK and transglutaminases, and possibly dopamine release, causing scleral remodelling or strengthening, leading to a reduction in axial length and vitreous chamber depth and consequently a suppression of myopia progression.

Clinical trials

Efficacy data submitted in support of atropine treatment to prevent or reduce the progression of myopia in children and adolescents was provided as published literature. The data were provided in 32 published articles evaluating the safety and/or efficacy of atropine eye drops when used to manage myopia in children and adolescents. Most studies were conducted in Asian children. The individual publications use a range of atropine concentrations ranging from high dose 1% through to very low dose 0.01% drops. The individual studies evaluated not only the initial response to treatment, but in some cases myopia rebound upon discontinuation, and response seen after re-introduction of treatment. This overview will focus of the key clinical studies relevant to the 0.01% formulation.

Chia 2012 (ATOM 2) is a randomised, double blind, three arm, active control, parallel group study which compared the rate of myopia progression in 400 children with myopia (mean refractive error -4.5 to -4.8 D) aged 6 to 12 years treated with 0.5%, 0.1% or 0.01% atropine eye drops for 2 years. The 0.01% strength was originally included as a non-active control as it was assumed to have minimal effect. Follow on studies by Chia 2014 reported the outcome of treatment discontinuation on myopia rebound, while Chia 2016 assessed the impact of re-introducing active treatment with very low dose atropine (0.01% drops). The total treatment period for the ATOM 2 series of studies was 5 years.

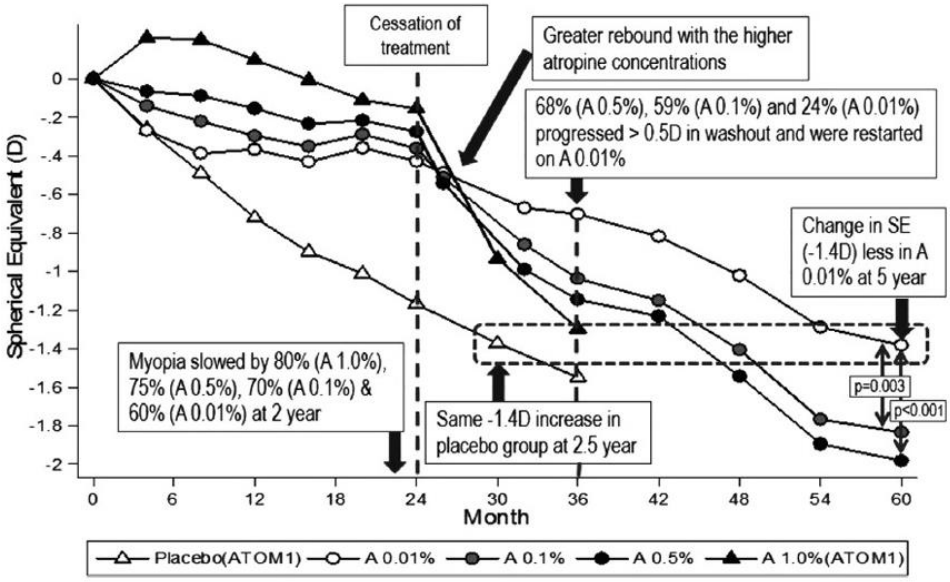
The final mean myopia progression over 2 years was -0.49 ± 0.60, -0.38 ± 0.60, and -0.30 ± 0.63 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($p = 0.07$), with a significant difference only between the 0.01% and 0.5% groups ($p< 0.05$). The percentage of children who recorded mild myopia progression at 2 years was 50% in the 0.01% group, 58% in the 0.1% group and 63% in the group treatment with 0.5% atropine drops. Mean change in AL at 2 years was 0.41 ± 0.32 mm for 0.01%, 0.28 ± 0.27 mm for 0.1% and 0.27 ± 0.25 mm for 0.5%.

Upon cessation of atropine treatment, a myopic rebound was observed by Chia 2014 in all 3 groups, however the rebound was significantly greater ($p< 0.001$) in the 0.5% group (-0.87 ± 0.52 D) compared to the 0.1% (-0.68 ± 0.45 D) and 0.01% group (-0.28 ± 0.33 D).

The increase was greatest over the first 8 months, slowing over the next 4 months. Similarly, there was a significant increase in AL ($p< 0.0001$) in the 0.5% group (0.35 mm) and 0.1% group (0.33 mm) compared to the 0.01% group (0.19 mm).

Chia 2016 demonstrated that fewer children in the 0.01% group (24%) required retreatment compared with children in the 0.1% (59%) and 0.5% group (68%). By year 5, overall progression of myopia was less in the 0.01% group (-1.38 ± 0.98 D) compared to with the 0.1% (-1.83 ± 1.16 D, $p = 0.003$) and 0.5% (-1.98 ± 1.10 D, $p< 0.001$). This was primarily due to fewer children in the 0.01% group progressing after treatment was stopped, and the rate of progression in the washout year in those who needed retreatment was also less in the 0.01% group compared to the 0.1 and 0.5% groups (-0.63, -0.94 and -1.09 D respectively (Figure 1).

Figure 1: The change in spherical equivalent observed during the ATOM 1 and ATOM 2 studies, following initial treatment with a range of atropine (A) concentrations, following a 12 month non treatment, washout period, and after retreatment with 0.01% atropine.



Yam 2018 (LAMP study) was a randomised, double blind, four arm, placebo control, parallel group study which compared the rate of myopia progression in 438 children with myopia (mean refractive error -3.71 to -3.98 D) aged 4 to 12 years treated with 0.05%, 0.025% or 0.01% atropine eye drops and placebo drops over 12 months of treatment. Ocular adverse

events were also reported. The overall design was very similar to that used in the ATOM study series.

The final mean myopia progression at the end of 12 month's treatment was -0.27 ± 0.61, -0.46 ± 0.45, and -0.59 ± 0.61 D in the atropine 0.05%, 0.025%, and 0.01% groups, and -0.81 ± 0.53 D in the placebo group respectively ($p< 0.001$). The difference between each group was also significant for each pair wise comparison. At 12 months, 69.6%, 51.6% and 43.8% of participants in the 0.05%, 0.025% and 0.01% treatment groups progressed by <0.5 D, compared to 24.2% in the placebo group.

Similarly, the change in AL was larger in the placebo group (0.41 ± 0.22 mm) than in the 0.05% (0.20 ± 0.25 mm), 0.025% (0.29 ± 0.20 mm) and 0.01% (0.36 ± 0.29 mm) atropine groups ($p< 0.001$). The difference between placebo and 0.01% group was not significant, however for all other pair wise comparisons between active treatment groups the difference was statistically significant ($p< 0.001$).

Yam 2019 (Phase 2 report) was a randomised double-blind trial extended from the LAMP study that included 483 children aged 4–12 with myopia of at least -1.0 diopter (D). Children in the initial placebo group were switched to receive 0.05% atropine from the beginning of the second year follow-up, whereas those in the 0.05%, 0.025%, and 0.01% atropine groups continued with the same regimen. Changes in spherical equivalent (SE) and AL and their differences between groups was the main outcome measure.

Over the 2-year period, the mean SE progression was 0.55_0.86 D, 0.85_0.73 D, and 1.12_0.85 D in the 0.05%, 0.025%, and 0.01% atropine groups, respectively ($p=0.015$, $p< 0.001$, and $p = 0.02$, respectively, for pairwise comparisons), with mean AL changes over 2 years of 0.39±0.35 mm, 0.50±0.33 mm, and 0.59±0.38 mm ($p=0.04$, $p<0.001$, and $p=0.10$, respectively). Compared with the first year, the second-year efficacy of 0.05% and 0.025% atropine remained similar ($p> 0.1$) but improved mildly in the 0.01% atropine group ($p = 0.04$). For the phase 1 placebo group, the myopia progression was reduced significantly after switching to 0.05% atropine (SE change, 0.18 D in second year vs 0.82 D in first year [$p< 0.001$]; AL elongated 0.15 mm in second year vs 0.43 mm in first year [$p< 0.001$]). Accommodation loss and change in

pupil size in all concentrations remained similar to the first-year results and were well tolerated. Visual acuity and vision-related quality of life remained unaffected.

5.2 Pharmacokinetic properties [1.11]

Absorption

Atropine is readily absorbed from the gastrointestinal tract; it is also readily absorbed from mucous membranes, the eye, and to some extent through intact skin.

Following the instillation of 30 microlitres of 1% atropine sulfate ophthalmic solution (0.3 mg) into the lower cul-de-sac of one eye in young health volunteers, the average ocular bioavailability was estimated as 63.6 ± 28.6%. No cardiovascular changes were observed.

Distribution

It is rapidly cleared from the blood and is distributed throughout the body. It crosses the blood-brain barrier.

Metabolism

It is incompletely metabolised in the liver.

Excretion

It is excreted in the urine as unchanged drug and metabolites. A half-life of 4 hours has been reported.

5.3 Preclinical safety data [1.12]

Genotoxicity

Available data are limited but indicate a lack of genotoxicity for atropine. Mutagenicity in bacteria and clastogenicity in vitro in human cells were not observed.

Carcinogenicity

No data available.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride

Boric acid

Hypromellose

Hydrochloric acid

Sodium hydroxide

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.

Discard 24 hours after opening.

6.5 Nature and contents of container

LDPE plastic tube 0.3 and 0.5 mL packed in aluminium sachet of 10 tubes and packed in paper box of 3 sachets

7. Marketing authorization holder

Millimed BFS Co., Ltd.

174, 179 Moo 8, Pha Ngam, Wiang Chai,

Chiang Rai, 57210, Thailand.

Tel. 0 2945 9555

8. Marketing authorization number(s)

1A 107/67

9. Date of first authorization/renewal of the authorization

27 October 2024

10. Date of revision of the text

2 October 2024