Isopto® Carpine

Cholinergic agonist (miotic)

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Eye drops, solution

Slightly viscous, practically clear and practically colorless to pale yellow solution

Certain dosage strengths may not be available in all countries.

Active substance

Pilocarpine hydrochloride 2%

20 mg of pilocarpine hydrochloride in 1 mL solution (2%)

Excipients

Excipients with known effect: 1 mL of the eye drop solution contains 0.01% of benzalkonium chloride.

Other excipients: boric acid; hydroxypropyl methylcellulose; sodium citrate; sodium hydroxide and/or concentrated hydrochloric acid (for pH adjustment) and purified water.

INDICATIONS

Isopto Carpine contains pilocarpine hydrochloride, a miotic (parasympathomimetic).

Isopto Carpine ophthalmic solution is used to control intraocular pressure in chronic simple glaucoma. In acute glaucoma it may be used alone prior to emergency surgery, or in combination with other miotics or carbonic anhydrase inhibitors. Patients can be maintained on Isopto Carpine ophthalmic solution as long as intraocular tension is controlled and there is no visual deterioration as indicated by changes in the visual field.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

2 drops topically in the eye(s) 3 times daily or as directed by a physician.

Special populations

Renal and hepatic impairment

- Safety and efficacy of Isopto Carpine in patients with hepatic or renal impairment have not been established.

Pediatric patients (below 18 years)

- Safety and efficacy of Isopto Carpine in pediatric patients have not been established. Due to a lack of pharmacokinetic data for the pediatric population, it is not possible to make particular evidence-based dose recommendations for children.

Geriatric patients (65 years of age or above)

- No overall differences in safety and efficacy have been observed between elderly and younger patients.

Method of administration

- For ocular use.
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.
- If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.
- Nasolacrimal occlusion or gently closing the eyelid for 2 minutes after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Miotics are contraindicated in conditions where papillary constriction is undesirable such as acute iritis or anterior uveitis.

WARNINGS AND PRECAUTIONS

- Retinal detachment has been reported when miotics are used in susceptible individuals, such as young patients with myopia or patients with history of retinal detachment. Fundus examination is advised prior to initiation of treatment with Isopto Carpine.
- Miotics should be avoided in acute inflammatory disease of the anterior chamber.
- A paradoxical rise in IOP may be observed in patients with severely compromised trabecular outflow.
- Caution is advised in the presence of corneal or conjunctival damage to avoid excessive penetration which can produce systemic toxicity.
- Isopto Carpine should be used with caution in patients with acute cardiac failure, bronchial asthma, peptic ulcer, hyperthyroidism, gastro-intestinal spasm, Parkinson's disease, urinary tract obstruction, recent myocardial infarction, hypertension and hypotension due to the risk of exacerbating these conditions.
- Isopto Carpine contains benzalkonium chloride which may cause eye irritation and is known to discolor soft contact lenses. Patients should avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Isopto Carpine and to wait at least the 15 minutes before reinsertion.

Driving and using machines

Isopto Carpine has a major influence on the ability to drive and use machines. Miosis may cause blurred vision and difficulty in dark adaptation. Patients should be advised to exercise caution while driving at night or while performing hazardous tasks in poor light.

ADVERSE DRUG REACTIONS

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reactions	Frequency category
Nervous system disorders	Headache	Very common
	Dizziness	Common
Eye disorders	Blurred vision	Very common
	Vitreous floaters, visual acuity reduced, eye pain, photopsia, eye irritation, ocular hyperaemia	Common
	Retinal tear, vitreous hemorrhage, vitreous detachment, eyelid oedema, miosis, glare, foreign body sensation in eyes	Uncommon
Gastrointestinal disorders	Nausea	Common

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse reactions have been derived from post-marketing experience with Isopto Carpine via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Eye disorders	Intraocular pressure increased, corneal oedema
Gastrointestinal disorders	Vomiting

INTERACTIONS

No clinically relevant interactions have been described.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well controlled studies in pregnant women to inform a drug associated risk.

Reproductive studies in rats have demonstrated that oral administration of pilocarpine during organogenesis induced embryotoxicity at maternally toxic doses corresponding to 1366 times the maximum recommended ocular human dose (MROHD) based on plasma area under the curve (AUC) concentrations. Pilocarpine had no teratogenic potential in rats and rabbits up to the maximum tested dose levels (3188 times the MROHD based on plasma concentrations in rats and 5 times the MRHOD based on body surface area (BSA) in rabbits) (see Animal data).

Systemic exposure to pilocarpine in a pregnant woman is expected to be low following topical ocular administration (see section CLINICAL PHARMACOLOGY). However, the possibility of harm to the fetus cannot be ruled out. Advise pregnant women of a potential risk to a fetus. Isopto Carpine should be given to pregnant women only if clearly needed.

Data

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of pilocarpine up to 90 mg/kg/day and 9 mg/kg/day, respectively, during the period of organogenesis. Increased incidences of skeletal variations and reduction of the mean fetal body weight were observed in rats following prenatal exposure to pilocarpine at an oral dose of 90 mg/kg/day corresponding to more than 3188 times the MROHD [0.64 mg/kg/day] based on plasma AUC concentrations. These embryo-toxic effects may have been secondary to maternal toxicity. The no-observed-adverse-effect-level (NOAEL) for fetal developmental toxicity was determined to be 26 mg/kg/day. There was no evidence of a teratogenic effect at any of the tested doses in rats.

In an embryo-fetal development toxicity study in rabbits, pilocarpine was neither teratogenic nor embryo toxic up to the highest tested dose of 9 mg/kg/day (5 times the MROHD based on BSA).

In a pre- and postnatal development study, an increased incidence of stillbirth was observed in rats exposed to pilocarpine during gestation and lactation at an oral dose of 36 mg/kg/day (3188 times the MROHD based on plasma AUC). Decreased neonatal survival and reduced mean body weight

of pups were observed in this study at doses of 18 mg/kg/day (1366 times the MROHD based on plasma AUC) and above. Maternal toxicity was observed at doses of 18 and 36 mg/kg/day. The observed effects may have been secondary to maternal toxicity. The NOAEL for pup growth was determined to be 3 mg/kg/day (168 times the MROHD based on plasma AUC).

Lactation

Risk summary

There are no data on the effects of pilocarpine on the breastfed child or on milk production. It is not known if pilocarpine is transferred into human milk. Pilocarpine was transferred into the milk of lactating rats after oral administration (see Data).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for using Isopto Carpine and any potential adverse effects on the breast-fed child from use of Isopto Carpine.

Data

Animal data

After a single oral dose (0.3 mg/kg) of ^{14}C-pilocarpine to lactating rats at 14 days following parturition, ^{14}C was identified in the milk. At 0.5 hour, similar concentrations of ^{14}C were observed in the milk (123 ng.eq/g) and plasma (126 ng.eq/g) of nursing rats. At 8 hours, the ^{14}C concentrations in the milk and plasma were 8 ng.eq/g and 4 ng.eq/g respectively which translates to a milk to plasma ratio of two. These concentrations declined subsequently, at similar rates, but were still detectable at 24 hours.

Females and males of reproductive potential

Infertility

There is no data on the effect of pilocarpine on human fertility. In animal fertility studies, pilocarpine did affect fertility in male and female rats at doses greater than or equal to 168-times the MROHD based on plasma AUC concentrations (see Section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

In case of overdose or accidental ingestion, symptoms of toxicity may include headache, salivation, sweating, syncope, bradycardia, hypotension, abdominal cramps, vomiting, asthma and diarrhea.

Treatment of overdose is supportive. In cases of severe systemic toxicity therapy with anticholinergics may be necessary.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pilocarpine hydrochloride is a direct acting cholinergic parasympathomimetic agent with a dominant action at muscarinic sites both peripherally and centrally. Like other choline esters, pilocarpine affects the cardiovascular system, exocrine glands, and smooth muscle. Although the precise mechanism by which pilocarpine reduces IOP has not been established, the most widely accepted explanation involves direct stimulation of the longitudinal muscle of the ciliary body, which in turn causes the scleral spur to widen the trabecular spaces and increase aqueous outflow. Pilocarpine appears to reduce IOP to the same degree in both healthy and glaucomatous eyes, including those with ocular hypertension. In each case pilocarpine reduces IOP approximately 10% to 40%.

Pharmacokinetics (PK)

Absorption

Systemic exposure to pilocarpine was evaluated in 14 healthy subjects administered 2 drops of Isopto Carpine ophthalmic solution 4% to both eyes 4 times daily for 8 days. A comparison of maximal plasma concentration (C_{max}) values on Days 5 and 8 indicated that pilocarpine concentrations in plasma reached steady-state following topical administration of Isopto Carpine 4%. The mean (SD) C_{max} and $AUC_{0\text{-}last}$ values on Day 8 were 3.7 (3.2) ng/mL and 7.7 (8.4) ng×hour/mL, respectively. The T_{max} values on Day 8 ranged from 0.5 to 1 hour.

Oral administration of pilocarpine to 3 healthy male volunteers as a solution or capsules showed that pilocarpine was rapidly absorbed into the blood stream and was measured in saliva following administration. Approximately 60% of the pilocarpine administered was absorbed ingestion of a solution or capsules of pilocarpine.

Distribution

In rabbits, topical ocular administration of pilocarpine showed the drug reached a peak concentration in the cornea within 5 minutes and in the aqueous humor within 20 minutes. Up to 80% of the total pilocarpine content of the cornea was in the epithelium.

Oral (PO) administration of ^{14}C-pilocarpine to rats showed that, excluding organs and tissues associated with absorption or elimination, most tissues concentrations were similar to, or less than the corresponding plasma concentration.

Experiments on the uptake of pilocarpine by ocular melanin showed that the pigment present in uveal tissue of pigmented rabbits is responsible for most of the uptake or inactivation of pilocarpine. These findings suggest that in the clinical situation some of the pilocarpine administered may be bound by uveal pigmented tissue.

Biotransformation/metabolism

In 2 clinical studies, it was shown that pilocarpine is metabolized to pilocarpic acid by plasma esterase and to 3-hydroxypilocarpine by CYP2A6 and that genetic polymorphisms of the CYP2A6 gene influence the pharmacokinetic profiles of pilocarpine and its metabolites. These metabolites are pharmacologically inactive and extremely weak compared with pilocarpine.

Pilocarpine hydrolase activities in human liver microsomes and plasma were stimulated by the addition of CaCl2, suggesting that the calcium dependent esterase, paraoxonase 1 (PON1), was responsible for pilocarpine hydrolysis. Data supports human PON1 is responsible for the pilocarpine hydrolysis and that PON1 polymorphism would affect the pilocarpine hydrolase activity.

Elimination

Following oral administration pilocarpine and its metabolites (pilocarpic acid, and 3-hydroxypilocarpine) were detected in human blood and excreted into the urine at approximately equal levels. Pilocarpine excretion in urine was complete within 8 hours of administration.

Linearity/non-linearity

The linearity of pilocarpine pharmacokinetics had not been studied in human. In rats, administration of pilocarpine hydrochloride intraduodenally (0.1, 0.2, 0.4, and 0.8 mg/kg) induced salivary secretion from the submandibular/sublingual (SM/SL) glands in a dose-dependent manner.

Pharmacokinetic/pharmacodynamics relationships

Ocular pigmentation influences the ocular hypotensive response. Blue eyes demonstrate maximal ocular hypotensive responses, whereas darkly pigmented eyes demonstrate a relative resistance to IOP reduction. This dose-response effect should be considered when treating darkly pigmented

subjects with glaucoma. These patients may require pilocarpine solutions in concentrations exceeding 4%.

Human patients receiving topical ocular pilocarpine showed that baseline outflow facility and maximum pilocarpine induced refractive change (i.e., accommodation) declined with age, but the decrease in IOP and the facility response to pilocarpine did not.

Special populations

Pediatric patients (below 18 years)

There is limited data on the use of pilocarpine in the pediatric population. Published literature does not contradict the use of pilocarpine in pediatric patients (see section DOSAGE REGIMEN AND ADMINISTRATION).

CLINICAL STUDIES

Isopto Carpine is a well-established product.

NON-CLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional repeated dose toxicity and genotoxicity studies.

Pilocarpine was not carcinogenic in mice but induced benign pheochromocytomas in rats at a dose of 18 mg/kg/day. Analysis of genotoxicity studies, tumor type and its incidence led to the conclusion that chronic pilocarpine use does not represent a significant risk for carcinogenicity in humans. In addition, pilocarpine exposure (plasma AUC) at the no effect dose for increased incidence pheochromocytomas in rats (9 mg/kg/day) is greater than 650-fold the MROHD, further emphasizing that this is not relevant for clinical ocular use.

For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Effects of pilocarpine on the male reproductive system were observed in three species (mouse, rat and dog).

In mice, there were macroscopic and microscopic findings on testes and bulbourethral glands at all oral dose levels (3, 10, and 30 mg/kg/day) tested in a 104-week carcinogenicity study. The lowest dose of 3 mg/kg/day corresponds to dose multiples of about 207-fold when compared to MROHD based on C_{max}.

In male and female rats, oral administration of pilocarpine at a dose of 18 mg/kg/day (and higher) resulted in impaired reproductive function, including reduced fertility, prolonged diestrus, decreased sperm motility, and morphologically abnormal sperm. The NOAEL was determined to be 3 mg/kg/day, which corresponds to 168-fold the MROHD based on plasma AUC.
In repeated-dose toxicity studies, dogs exposed to pilocarpine at an oral dose of 3 mg/kg/day for six months showed evidence of impaired spermatogenesis. This corresponds to about 174-fold the MROHD based on plasma C_{max}.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Store below 30°C.

Isopto Carpine should not be used after the date marked "EXP" on the pack.

Isopto Carpine must be kept out of the reach and sight of children.

INSTRUCTIONS for USE AND HANDLING

No special requirements.

PRODUCT REGISTRATION HOLDER

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