BETOPTIC®, BETOPTIC S®

Antiglaucoma preparations and miotics, beta-blocking agents

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Eye drops, solution

Eye drops, suspension

Certain dosage strengths and dosage forms may not be available in all countries.

Active substance(s)

Eye drops, solution 0.5%

1 mL of solution contains 5.6 mg betaxolol hydrochloride, equivalent to 5 mg betaxolol.

Eye drops, suspension 0.25%

1 mL of suspension contains 2.8 mg betaxolol hydrochloride, equivalent to 2.5 mg betaxolol.

Eye drops, suspension 0.5%

1 mL of suspension contains 5.6 mg betaxolol hydrochloride, equivalent to 5 mg betaxolol.

Excipients

Eye drops, solution 0.5%

Sodium chloride, benzalkonium chloride, disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

Eye drops, suspension 0.25%

Mannitol, poly (styrene-divinylbenzene) sulfonic acid, carbomer 934P, benzalkonium chloride disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

Eye drops, suspension 0.25%

Mannitol, carbomer 974P, boric acid, poly(styrene-divinylbenzene) sulfonic acid, N-Lauroylsarcosine, benzalkonium chloride, disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

Eye drops, suspension 0.25% (Single Dose)

Mannitol, poly (styrene-divinylbenzene) sulfonic acid, carbomer 974P, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

Eye drops, suspension 0.5%

Mannitol, poly (styrene-divinylbenzene) sulfonic acid, carbomer 934P, benzalkonium chloride, disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Betoptic Eye drops, solution or Betoptic S Eye drops, suspension is indicated for the reduction of elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Adults

• For Betoptic Eye drops suspension 0.25%, the recommended dose is 1 to 2 drops in the affected eye(s) twice daily.

• For Betoptic Eye drops, solution and Betoptic Eye drops, suspension 0.5%, the recommended dose is 1 drop in the affected eye(s) twice daily.

• In some patients, the intraocular pressure lowering responses to Betoptic Eye drops, solution and Betoptic S Eye drops, suspension may require a few weeks to stabilize. A final assessment and evaluation of the intraocular pressure-lowering effect should not be carried out until about a month of treatment has been given.

• If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with other anti-glaucoma agents can be instituted.

Special populations

Renal and hepatic impairment:

- Safety and efficacy in patients with renal and hepatic impairment have not been studied.

Pediatric patients (below 18 years)

• Betoptic 0.5% is not recommended in pediatric patients as experience is limited only to use of Betoptic 0.25%.

• Limited clinical data are available regarding the safety and efficacy of Betoptic 0.25% in pediatric patients.

• Clinicians should thoroughly evaluate the risks and benefits when considering medical therapy with Betoptic 0.25% in pediatric patients. A detailed pediatric history and examination to determine possible systemic abnormalities should precede the use of Betoptic S 0.25%. If the expected benefit outweighs the risk, it may be considered to use the lowest dose of 1 drop of Betoptic 0.25% once daily. If intraocular pressure cannot be sufficiently controlled, a careful titration up to a maximum of 2 drops daily per affected eye should be considered. If applied twice daily, an interval of 12 hours is recommended.

• Patients, especially neonates, should be closely observed after the first dose for 1 or 2 hours in the clinic and closely monitored for ocular and systemic side effects until surgery is performed.

Geriatric patients (65 years or above)

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

Method of administration

- For ocular use only

- Shake well before use [applicable for Betoptic S Eye drops, suspension 0.25%]
- After cap is removed, if tamper evident snap collar is loose, remove the snap collar before using the product. [Only applicable for eye drop containing a snap collar]
- Nasolacrimal occlusion and closing the eyelids for 2 minutes after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse drug reactions.
- 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 medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.
-

CONTRAINDICATIONS

- Hypersensitivity to the active substance, or to any of the excipients.
- Sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock.

WARNINGS AND PRECAUTIONS

General

Like other topically applied ophthalmic agents, betaxolol is absorbed systemically. Due to the beta-adrenergic component in ophthalmic betaxolol, the same types of cardiovascular, pulmonary and other adverse drug reactions seen with systemic beta-adrenergic blocking agents may occur.

Cardiac disorders

In patients with cardiovascular diseases (e.g., coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and adverse drug reactions.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

Hypoglycemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Hyperthyroidism

Beta-blockers may mask the signs of hyperthyroidism.

Muscle weakness

Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

Anaphylactic reactions

While taking beta-blockers, patients with history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Surgical anesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g., of adrenaline. The anesthesiologist should be informed if the patient is receiving betaxolol.

Special excipients

Betoptic/ Betoptic S contains benzalkonium chloride which may cause eye irritation and is known to discolor soft contact lenses. Patients should avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of Betoptic Eye Drops, solution and Betoptic S Eye Drops, suspension and to wait at least 15 minutes before reinsertion. [Only applicable for eye drops containing benzalkonium chloride]

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

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) and very rare (< 1/10,000).

Table 1 Adverse drug reactions from clinical trials

System organ classification (SOC)	Adverse drug reactions	Frequency category
Psychiatric disorders	Anxiety	Rare
Nervous system disorders	Headache	Common
	Syncope	Rare
Eye disorders	Ocular discomfort	Very common
	Vision blurred, lacrimation increased	Common
	Punctate keratitis, keratitis, conjunctivitis, blepharitis, visual impairment, photophobia, eye pain, dry eye, asthenopia, blepharospasm, eye pruritus, eye discharge, eyelid margin crusting, eye inflammation, eye irritation, conjunctival disorder, conjunctival oedema, ocular hyperaemia	Uncommon
	Cataract	Rare
Cardiac disorders	Bradycardia, tachycardia	Uncommon
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Asthma, dyspnoea, rhinitis	Uncommon
	Cough, rhinorrhoea	Rare
Gastrointestinal disorders	Nausea	Uncommon
	Dysgeusia	Rare
Skin and subcutaneous tissue disorders	Dermatitis, rash	Rare
Reproductive system and breast disorders	Libido decreased	Rare

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

The following adverse drug reactions have been derived from post-marketing experience with betaxolol eye drops 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 class in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

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

System organ classification (SOC)	Adverse drug reactions
Immune system disorders	hypersensitivity
Psychiatric disorders	insomnia, depression
Nervous system disorders	dizziness
Eye disorders	erythema of eyelid
Cardiac disorders	arrhythmia
Skin and subcutaneous tissue disorders	alopecia
General disorders and administration site conditions	asthenia

INTERACTIONS

• There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers are administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone) or digitalis glycosides.

• Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section WARNINGS AND PRECAUTIONS).

PREGNANCY, LACTATION, FEMALES AND MALE OF REPRODUCTIVE POTENTIAL

Pregnancy Risk summary

There are no adequate and well-controlled studies in pregnant women regarding the ocular use of Betoptic/Betoptic S.

Epidemiological studies have not revealed malformative effects, but show a risk for intra-uterine growth retardation when beta-blockers are administered orally. In addition, signs and symptoms of beta-blockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when systemic beta-blockers have been administered to the mother until delivery.

Studies in rats and rabbits with betaxolol have shown embryo-fetal toxicity.

Betoptic/Betoptic S should not be used during pregnancy unless clearly necessary. However, if Betoptic/Betoptic S is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Data Animal Data

Reproduction, teratology, and peri- and postnatal studies with orally administered betaxolol hydrochloride in rats and rabbits showed evidence of drug-related post-implantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol hydrochloride was not shown to be teratogenic.

Lactation Risk summary

There is limited data regarding the use of Betoptic/Betoptic S in breast-feeding women.

It is not known whether betaxolol is transferred into human milk following topical ocular administration. Betaxolol is transferred into human milk following oral administration. Oral beta-blockers have the potential to cause serious adverse drug reactions in the breast-fed infant. However, in the case of ocular administration of betaxolol at therapeutic doses, it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Betoptic/Betoptic S and any potential adverse effects on the breast-fed child from Betoptic/Betoptic S.

Females and males of reproductive potential Infertility

There are no data on the effects of Betoptic/ Betoptic S on human fertility.

OVERDOSAGE

In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

If overdose with Betoptic/ Betoptic S occurs, treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Betaxolol hydrochloride, a cardioselective (beta-1-adrenergic) receptor blocking agent, does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Upon instillation in the eye, Betoptic S Eye drops, suspension reduces elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. The mechanism of ocular hypotensive action appears to be a reduction of aqueous production. The onset of action with Betoptic S Eye drops, suspension can generally be noted within 30 minutes and the maximal effect can be usually noted at 2 hours after topical administration. A single dose provides a 12-hour reduction in intraocular pressure.

Betoptic Eye drops, suspension's action as a neuroprotective agent has been shown in both *in vivo* and *in vitro* experiments in rabbit retina, rat cortical cultures and chick retinal cultures.

Pharmacodynamics (PD)

The polar nature of betaxolol can produce apparent ocular irritation. In the current formulation, molecules are ionically bound to the amberlite resin. Upon instillation, these molecules are displaced by sodium ions in the tear film. This displacement process occurs over several minutes and enhances the ocular comfort. Betoptic S Eye drops, suspension has little or no effect on the constriction of the pupil. The peripheral vasorelaxing action of Betoptic S Eye drops, suspension has been shown in dogs, while the vasorelaxing and calcium channel blocking actions of Betoptic S Eye drops, suspension have been demonstrated in several *in vivo* studies utilizing both non-ocular and ocular vessels from rat, guinea pig, rabbit, canine, porcine and bovine models. Betoptic Eye drops, suspension causes local constriction of the ciliary arterioles of rabbits (decreasing after administration during 50 days).

Betoptic Eye drops, suspension may be absorbed systemically possibly causing the same adverse drug reactions as the orally administered drug. Oral beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor antagonists may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function. No evidence of cardiovascular beta-adrenergic-blockade during exercise was observed in a study involving normal subjects comparing ophthalmic Betoptic Eye drops, suspension and placebo for effects on blood pressure and heart rate. [*Betoptic S Eye drops, suspension 0.25%*]

Pharmacokinetics (PK) Absorption

Following oral or intravenous administration, betaxolol plasma concentrations decline with a terminal half-life of 15 to 16 hours. Oral bioavailability is about 80%. Following a 20 mg oral dose, a mean maximum plasma concentration of about 46 ng/mL was achieved at 4 hours. Plasma drug levels increase in a dose-proportional manner.

Following topical ocular administration of 0.5% Betoptic solution to normal volunteers for 1 week, maximum steady-state plasma drug concentrations were about 1 ng/mL or less.

Distribution

Following multiple topical ocular doses to pigmented rabbits, highest ocular exposure was observed in aqueous humor, iris-ciliary body and retina with mean maximum steady-state concentrations of 776, 32,500 and 18 ng/g, respectively. Exposure in retina and other posterior tissues was due to both local absorption and redistribution from the systemic circulation. Plasma drug levels were low (3 mg/mL or less).

Biotransformation/metabolism

In humans, betaxolol is primarily metabolized to two carboxylic acid derivatives: one formed by elimination of the cyclopropyl-methyl group and hydroxylation of the remaining terminal carbon followed by oxidation of this alcohol (24% of dose), the other formed by oxidation of the carbon α to the isopropyl-amino moiety, with elimination of the latter (35% of dose). Phase II metabolism of betaxolol and its metabolites by conjugation reactions is negligible.

Elimination

Betaxolol is eliminated primarily in the urine (80-90% of dose), with 16% of the dose as parent drug and the remainder being the two primary metabolites and small amounts of minor metabolites.

CLINICAL STUDIES

In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of Betoptic S Eye drops, suspension 0.25% and 0.5% were clinically equivalent. Clinical studies show that topical Betoptic S Eye drops, suspension reduces mean intraocular pressure 25% from baseline. In trials using 22 mmHg as a generally accepted index of intraocular pressure control, Betoptic S Eye drops, suspension was effective in more than 94% of the population studies, of which 73% were treated with the beta blocker alone. Data obtained during controlled clinical trials in patients with chronic open-angle glaucoma and ocular hypertension indicates that treatment with Betoptic S Eye drops, suspension has a superior long-term benefit on the visual field as compared to treatment with timolol, a non-selective beta-blocker. In a 3-way masked crossover studies comparing ophthalmic Betoptic S Eye drops, suspension to timolol and placebo, Betoptic S Eye drops, suspension was found to have minimal effect on pulmonary and cardiovascular parameters. In contrast, timolol significantly decreased pulmonary function and produced a lowering of the mean heart rate.

Additionally, during therapy with Betoptic S Eye drops, suspension, no negative effect on the blood supply to the optic nerve has been observed. Rather, Betoptic S Eye drops, suspension maintained or improved ocular blood flow/perfusion. Clinical observation of glaucoma patients treated with Betoptic S Eye drops, suspension for up to 3 years shows that the intraocular pressure lowering effect is well maintained.

Betoptic S Eye drops, suspension does not produce miosis or accommodative spasm, as frequently seen with miotic agents. The blurred vision and night blindness often associated with standard miotic therapy are not associated with ophthalmic Betoptic S Eye drops, suspension. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil. Betoptic S Eye drops, suspension has been used successfully in glaucoma patients who have undergone laser trabeculoplasty and have needed additional long-term hypotensive therapy. Betoptic S Eye drops, suspension has also been well tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

Pediatric population

In a randomized clinical study involving 35 pediatric patients, twice daily Betoptic S 0.25% ophthalmic suspension was effective in reducing intraocular pressure.

NON-CLINICAL SAFETY DATA

Non-clinical data for betaxolol reveal no special hazard for humans based on conventional studies of repeated dose toxicity. In a battery of standard in vitro and in vivo studies, betaxolol was not genotoxic.

Lifetime studies with betaxolol hydrochloride in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at oral doses of 3, 12 or 48 mg/kg/day demonstrated no carcinogenic potential.

Reproductive toxicity

See section PREGNANCY, LACTATION AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Juvenile animal studies

No preclinical studies have been conducted to specifically address risks related to administration to juvenile animals.

INCOMPATIBILITIES

Not applicable

STORAGE

See folding box.

Store the bottle in the outer carton in order to protect from light.

Betoptic, Betoptic S should not be used after the date marked "EXP" on the pack.

Betoptic, Betoptic S must be kept out of the reach and sight of children.

INFORMATION FOR PATIENTS

Eye drops, solution

No special requirements.

Eye drops, suspension

Shake before use.

Eye drops, suspension unit dose containers

Shake before use.

This product is preservative-free, therefore do not reuse. Discard single dose dispenser after use.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer:

Alcon Couvreur
NV Rijksweg 14, 2870
Puurs Belgium

MAH:

Novartis Nigeria Limited

Landmark Building,

52-54, Isaac John Street,

Ikeja G.R.A

Lagos.

Information issued: November-2022

 = registered trademark

Novartis Pharma AG, Basel, Switzerland