SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BETOPTIC 5 mg/ml eye drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 5 mg betaxolol base (equivalent to 5.6 mg betaxolol hydrochloride).
Excipient with known effect: this medicine contains 0.1 mg benzalkonium chloride in each ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BETOPTIC is indicated in adult patients with chronic open-angle glaucoma. It may be used alone or in combination with other intraocular pressure lowering medications.

4.2 Posology and method of administration

Posology

Adults (including elderly)
The usual dose is one drop in the affected eye(s) twice daily.
In some patients, the intraocular pressure lowering response may require a few weeks to stabilise. The intraocular pressure should therefore be determined during the first month of treatment. Thereafter, the frequency of measurement should be determined by the physician. Because of variations of intraocular pressure in some patients, satisfactory response to twice a day therapy is best determined by measuring intraocular pressure at different times during the day.

If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with other intraocular pressure lowering medications (including pilocarpine, other miotics, adrenaline, or systemically administered carbonic anhydrase inhibitors) can be instituted.

Therapy should be individualised for optimal control of glaucoma in each patient.

To switch a patient from a single anti-glaucoma agent to a treatment with BETOPTIC eye drops, continue the initial medication and add one drop of BETOPTIC eye drops twice a day. On the following day, discontinue the initial medication completely and continue the treatment with BETOPTIC eye drops.

When a patient is switched from several concomitantly administered anti-glaucoma agents to a treatment with BETOPTIC eye drops, individualisation of the therapy is required.
Only adjust one agent at a time and at intervals of at least one week. A recommended approach is to continue the agents being used and to add one drop of BETOPTIC twice a day. Then, on the following day one of the other medicines is discontinued.

The remaining anti-glaucoma medicines may be decreased or discontinued according to the patient's response to the treatment. This decision is left to the judgement of the ophthalmologist.

Paediatric population
Due to limited data, betaxolol can only be recommended for use in primary congenital and primary juvenile glaucoma for a transitional period while a decision is made on a surgical approach and in case of failed surgery while considering further options.

The physician should carefully assess the risks and benefits when considering betaxolol therapy in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of betaxolol.
No specific dosage recommendation can be made as there are only limited clinical data (see also section 5.1). However, if the benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If the IOP cannot be sufficiently controlled, careful up-titration to a maximum of 2 drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours between administrations should be preferred.
Furthermore, patients, especially newborn infants, should be carefully observed after administration of the first dose for one to two hours in the ophthalmologist's office/hospital and monitored closely for ocular and systemic side effects until surgery is performed.

Duration of treatment:
Temporary use in paediatric patients (see also section 4.2 "Paediatric population").

Method of administration
After cap is removed, if tamper evident snap collar is loose, remove before using product.

Nasolacrimal occlusion or closure of the eyelids for 2 minutes decreases systemic absorption. This may result in reduced systemic side effects and increased local activity.

If more than one ophthalmic preparations are to be used, one should wait at least 5 minutes between two applications. Eye ointments should be administered last.

Use in hepatic and renal impairment
The safety and efficacy of BETOPTIC eye drops in patients with hepatic and renal impairment have not been established.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Reactive airway disorders, including severe bronchial asthma or a history of severe bronchial asthma, severe chronic obstructive pulmonary disease.
- Patients with sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with a pacemaker, known cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

General
- For ocular use only. Not for injection or ingestion.
- Like other topically applied ophthalmic agents, betaxolol is absorbed systemically. Due to its beta-adrenergic component, betaxolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce systemic absorption, see section 4.2 "Posology and method of administration".

- After application of the eye drops the following measures are useful to reduce systemic absorption:
  - Keep the eyelid closed for 2 minutes.
  - Close the lachrymal duct with a finger for 2 minutes.

Cardiac disorders

- Use with caution in patients with uncontrolled heart failure. When beginning therapy with betaxolol, patients with a history of severe cardiac disease should be monitored closely for signs of cardiac failure. Treatment with BETOPTIC should be discontinued at the first signs of cardiac failure.
- In patients with cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and adverse reactions.
- Due to their negative effect on conduction time, caution is required when beta-blockers are given to patients with first degree heart block.

Vascular disorders

- Because of potential effects of beta-blockers on blood pressure and heart rate (e.g. hypotension, bradycardia), use with caution in patients with cerebrovascular insufficiency, untreated phaeochromocytoma or metabolic acidosis, since beta-adrenergic blocking agents may adversely affect such diseases. If signs or symptoms suggesting reduced cerebral blood flow develop, consider alternative therapy.
- Patients with severe peripheral circulatory disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Hypoglycaemia/diabetes mellitus

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

Thyrotoxicosis

- Patients having or suspected of developing thyrotoxicosis should be monitored closely during ophthalmic betaxolol therapy, since beta-blockers may mask certain signs (e.g. tachycardia) and symptoms of hyperthyroidism and abrupt withdrawal of these agents can precipitate thyroid storm.

Respiratory disorders

- Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment.
- Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.
- Caution is required when treating patients with mild/moderate bronchial asthma, a history of mild/moderate bronchial asthma or mild/moderate chronic obstructive pulmonary disease (COPD).
- Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out.
  The risk of inducing bronchospasm must be appreciated in patients with symptomatic or poorly controlled asthma or obstructive airway diseases. Appropriate precautions, including consideration of alternative glaucoma therapies, should be taken.

Corneal diseases

- Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Muscle weakness

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

Surgical anaesthesia

- Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving betaxolol.
- Consideration should be given to the gradual withdrawal of beta-adrenergic receptor blocking agents prior to general anaesthesia because of reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Anaphylactic reactions

- While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction 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.

Choroidal detachment

- Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Other beta-blockers

- Betaxolol may interact with other medicinal products. The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when betaxolol is given to patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5 "Interaction with other medicinal products and other forms of interaction").

Ocular

- When BETOPTIC is used to reduce elevated intraocular pressure in closed angle glaucoma, it should be used with a miotic and not alone. In patients with closed angle glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil.

Paediatric population

- Betaxolol solutions should generally be used cautiously in young glaucoma patients (see also section 5.2).
- It is important to notify the parents of potential side effects so they can immediately discontinue therapy. Signs to look for are for example coughing and wheezing.
- Betaxolol must be used with extreme caution in neonates, infants and young children.

Contact lenses

- This medicine contains 0.1 mg benzalkonium chloride in each ml. Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Patients should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye).

4.5 Interaction with other medicinal products and other forms of interaction

- No specific drug interaction studies have been performed with betaxolol.
- Each interaction that is associated with systemically administered beta-blockers can, in principle, appear with the use of beta-blocker eye drops.

- There is a potential for additive effects resulting in hypotension and/or marked bradycardia, when eye drops with betaxolol are administered concomitantly with oral calcium antagonists, beta-blocking agents, anti-arrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine (see section 4.4). Orally administered beta-adrenergic blocking agents reduce cardiac output in healthy subjects and in 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.
- 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.
- Co-administration of ophthalmic beta-blockers with digitalis may have additive effects in prolonging atrioventricular conduction time. Close observation is recommended when a beta-adrenergic receptor inhibitor is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia which may result in dizziness, syncope, or postural hypotension.
- When used in conjunction with topical miotics and/or systemically administered carbonic anhydrase inhibitors, the effect of betaxolol eye drops in lowering IOP may be additive. In patients with angle-closure glaucoma, the immediate treatment objective consists in re-opening the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. Therefore, betaxolol eye drops should be used simultaneously with a miotic to reduce elevated intraocular pressure in angle-closure glaucoma (see section 4.4).
- Ophthalmic beta-blockers and phenothiazine compounds may have potential additive hypotensive effects due to mutual inhibition of metabolism.
- Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see Special warnings and precautions for use).
- As with the use of other antiglaucoma drugs, diminished responsiveness to BETOPTIC eye drops after prolonged therapy has been reported in some patients. However, in one long-term study in which 250 patients were followed for up to 3 years, no significant difference in mean intraocular pressure was observed after initial stabilisation.
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.
- Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline (see section 4.4).
- Oral beta-adrenergic blocking agents can enhance the rebound effect of hypertension which can occur when stopping the administration of clonidine. When the two substances are used simultaneously, the usage of the beta-adrenergic blocking agent should be stopped a few days before the progressive discontinuation of the clonidine therapy. When the treatment with the beta-adrenergic blocking agent replaces the clonidine therapy, it should be started a few days after the discontinuation of the clonidine therapy.
- If supplementary eye preparations are to be used, one should wait at least 5 minutes between two applications. Eye ointments should be administered last.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data for the use of betaxolol in pregnant women. Epidemiological studies have not revealed malformative effects, but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers had been administered until delivery.

Studies in rats and rabbits with betaxolol have shown reproductive toxicity (see section 5.3). Betaxolol should not be used during pregnancy unless clearly necessary, see section 4.2 "Posology and method of administration". However, if BETOPTIC is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breastfeeding
Beta-blockers are excreted in human milk, having the potential to cause serious undesirable effects in the infant of the nursing mother. However, at therapeutic doses of betaxolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2 "Posology and method of administration". It is unknown whether betaxolol is excreted in human milk following topical ocular administration. However, a risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from betaxolol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effects of BETOPTIC eye drops on human fertility. Studies in rats have shown effects on fertility following oral administration at oral doses of 32 and 256 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

BETOPTIC eye drops has no or negligible influence on the ability to drive and use machines. However, as with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines.

If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable Effects

Summary of the safety profile
In clinical trials, the most frequent adverse reaction associated with use of eye drops containing betaxolol was ocular discomfort, occurring in 12.0% of patients.

Tabulated list of adverse reactions
Like other topically applied ophthalmic medicinal products, betaxolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

The following adverse reactions are classified according to the following convention: 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), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions were obtained from clinical trials and spontaneous postmarketing reports.

System Organ Class	MedDRA Preferred Term
Immune system disorders	*Not known*: hypersensitivity, systemic allergic reactions including angio-oedema, urticaria, localised and generalised rash, pruritus, anaphylactic reaction
Metabolism and nutrition disorders	*Not known:* hypoglycaemia
Psychiatric disorders	*Rare*: anxiety *Not known*: insomnia, depression, nightmares, memory loss
Nervous system disorders	*Common:* headache

	Rare: syncope *Not known:* dizziness, cerebrovascular accident, cerebral ischaemia, increases in signs and symptoms of myasthenia gravis, paraesthesia
Eye disorders	*Very common:* ocular discomfort *Common:* vision blurred, lacrimation increased *Uncommon*: 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 (e.g. burning sensation, stinging sensation, itching, tearing, redness), conjunctival disorder, conjunctival oedema, ocular hyperaemia *Rare:* cataract, refraction disorder *Not known:* erythema of eyelid, choroidal detachment following filtration surgery (see section 4.4 "Special warnings and precautions for use"), decreased corneal sensitivity, corneal erosion, ptosis, diplopia
Cardiac disorders	*Uncommon:* bradycardia, tachycardia *Not known:* arrhythmia, chest pain, palpitations, oedema, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure
Vascular disorders	*Rare*: hypotension *Not known:* Raynaud's phenomenon, cold hands and feet
Respiratory, thoracic and mediastinal disorders	*Uncommon:* asthma, dyspnoea, rhinitis *Rare:* cough, rhinorrhea *Not known:* bronchospasm (predominantly in patients with pre-existing bronchospastic disease)
Gastrointestinal disorders	*Uncommon*: nausea *Rare:* dysgeusia *Not known:* dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	*Rare*: dermatitis, rash *Not known:* periorbital oedema, alopecia, psoriasiform rash or exacerbation of psoriasis
Musculoskeletal and connective tissue disorders	*Not known:* myalgia
Reproductive system and breast disorders	*Rare:* libido decreased *Not known:* sexual dysfunction
General disorders and administration site conditions	*Not known:* asthenia, fatigue

Description of selected adverse reactions

Since topically applied beta-adrenergic blocking agents may be absorbed systemically, adverse reactions found with systemic administration of $beta_1$-adrenergic blocking agents may occur with topical administration. These may include bradycardia, a slowed AV (atrioventricular) conduction or increase of an existing AV-block, hypotension, heart failure, cold and cyanotic extremities, Raynaud's phenomenon, paraesthesia of the extremities, increase of an existing intermittent claudication, fatigue, headache, impaired vision, hallucinations, psychoses, confusion, impotence, dizziness, sleep disturbances, depression, nightmares, gastrointestinal problems, nausea, vomiting, diarrhoea,

bronchospasm in patients with bronchial asthma or a history of asthmatic complaints, disorder of the skin, especially rash, and dry eyes. Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Paediatric population
The safety and IOP-lowering effect of BETOPTIC 0.25% has been demonstrated in paediatric patients in a 3-month, multi-centre, double-blind, active-controlled trial. The adverse event profile of BETOPTIC 0.25% was comparable to that seen in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

If ocular overdose occurs, flush eye(s) with water or normal saline (sodium chloride solution 0.9%). The most common signs and symptoms of overdose from systemic beta-blockers are bradycardia, hypotension, bronchospasm, and acute cardiac failure. If these occur, discontinue therapy and initiate appropriate symptomatic and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-glaucoma preparations and miotics, beta-blocking agents, ATC code: S 01 ED 02.

Mechanism of Action
Betaxolol hydrochloride is a cardioselective beta-blocker of the beta-adrenergic receptors. It does not have local anaesthetic (membrane-stabilising) activity and is devoid of sympathomimetic intrinsic action.

Orally administered 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.

Optic nerve head damage and visual field loss are the result of a sustained elevated ocular pressure and poor ocular perfusion. BETOPTIC eye drops with 0.5% of betaxolol, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma, and the mechanism of action of this reduction of intraocular pressure appears to be a reduction of aqueous production as demonstrated by tonography and fluorophotometry.

The onset of action with BETOPTIC eye drops can generally be noted within 30 minutes and the maximal effect can be detected two hours after topical administration.

A single dose provides a 12-hour reduction in intraocular pressure. Clinical observation of glaucoma patients treated with BETOPTIC eye drops for three years shows that the intraocular pressure-lowering effect was well-maintained.

Clinical studies demonstrated that BETOPTIC eye drops has, contrary to other beta blockers, a minimal effect on pulmonary and cardiovascular functions.

Betaxolol eye drops (1 drop in each eye) was compared to timolol and placebo in a random and masked crossover study challenging patients with reactive airway disease. Betaxolol hydrochloride has no significant effect on pulmonary function as measured by Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC) and the relation between both (FEV_1/FVC). Additionally, the action of isoproterenol, a beta stimulant, administered at the end of the study was not inhibited by betaxolol eye drops. In contrast, timolol eye drops significantly decreased these pulmonary functions.

FEV_1 Percent Change from Baseline

	Betaxolol 1.0%[a]	**Timolol 0.5%**	**Placebo**
Baseline	1.6	1.4	1.4
60 minutes	2.3	-25.7*	5.8
120 minutes	1.6	-27.4*	7.5
240 minutes	-6.4	-26.9*	6.9
Isoproterenol[b]	36.1	-12.4*	42.8

Schoene R.B. et al., Am. J. Ophthal., 97: 86, 1984.
[a]: twice the clinical concentration.
[b]: inhaled at 240 minutes; measurement at 270 minutes.
*: Timolol statistically different from betaxolol and placebo ($p<0.05$).

No evidence of cardiovascular beta-adrenergic-blockade during exercise was observed with betaxolol hydrochloride in a double-masked, crossover study in normal subjects comparing betaxolol eye drops, timolol eye drops and placebo for effects on blood pressure and heart rate. Mean arterial blood pressure was not affected by any treatment; however, timolol eye drops produced a significant decrease in the mean heart rate.

Mean Heart Rates

Bruce Stress Exercise Test Minutes	**Betaxolol 1%[a]**	**Timolol 0.5%**	**Placebo**
0	79.2	79.3	81.2
2	130.2	126.0	130.4
4	133.4	128.0*	134.3
6	136.4	129.2*	137.9
8	139.8	131.8*	139.4
10	140.8	131.8*	141.3

J.M. Atkins et al., Am. J. Ophthal. 99: 173-175, Feb., 1985
[a]: Twice the clinical concentration.
*: Mean pulse rate significantly lower for timolol than betaxolol or placebo ($p<0.05$).

Betaxolol eye drops 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.

Pharmacodynamic effects
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. The peripheral vasorelaxing action of betaxolol has been shown in an in vivo study in dogs, while the vaso-elaxing and calcium channel blocking actions of betaxololhave been demonstrated in several in vivo studies utilizing both non-ocular and ocular vessels from rat, guinea pig, rabbit, canine, porcine and bovine models. Betaxolol Eye Drops causes local constriction of the ciliary arterioles of rabbits (decreasing after administration during 50 days). Betaxolol may be absorbed systemically possibly causing the same undesirable effects as the orally administered drug. Oral beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart disease.

Clinical safety and Efficacy
Clinical studies show that BETOPTIC eye drops reduces intraocular pressure 25% from baseline. In trials using 22 mmHg as a generally accepted index of intraocular pressure control, BETOPTIC eye drops was effective in more than 94% of the population studied, 73% of which were treated with the beta-blocker alone. In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of BETOPTIC eye drops and timolol eye drops were clinically equivalent.

Betaxolol eye drops has also been used successfully in glaucoma patients that underwent laser trabeculoplasty and needed additional long-term ocular hypotensive therapy.

BETOPTIC eye drops does not produce miosis or accommodative spasm which are frequently seen with miotic agents. The blurred vision and night blindness often associated with standard miotic therapy are not associated with BETOPTIC eye drops.

Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil. As with any ophthalmic medication, temporary visual disturbance upon instillation may be experienced.

Paediatric population:
There are only very limited data available on the use of betaxolol 0.25% in the paediatric population for a treatment period up to 12 weeks. One small, double-blind, randomised, published clinical study conducted on 105 children (n=34 for betaxolol) aged 12 days - 5 years show to some extent evidence that betaxolol in the indication *primary congenital* and *primary juvenile glaucoma* is effective in short-term treatment (see section 4.2 and 4.4)

5.2 Pharmacokinetic properties

Absorption
Following oral or iv. 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 with increasing.
Following topical ocular administration of 0.5% betaxolol 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, 32500 and 18 ng/g, respectively. Exposure in retina and other posterior tissues was shown to

arise from both local absorption and redistribution from the systemic circulation. Plasma drug levels were low (3 ng/mL or less).

Biotransformation
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.

Paediatric population:
After topical administration in the eyes betaxolol is absorbed and reaches systemic circulation. In adults receiving a 40 µl dose of 0.5% betaxolol solution a mean maximum plasma concentration of 1.1 ± 0.8 ng/mL was observed. Due to a smaller distribution volume in children compared to adults a higher circulation concentration has to be taken into account. Because betaxolol elimination is primarily achieved by metabolisation, the immature metabolic enzyme pathways in neonates may result in an increased elimination half-life and increased blood levels with a greater risk of adverse events.

Hepatic Impairment, Renal Impairment and Geriatric Patients
Pharmacokinetic studies evaluating BETOPTIC eye drops, solution or suspensions in patients with hepatic and renal impairment and in geriatric patients have not been conducted. Since betaxolol is eliminated by metabolism and excretion, higher plasma levels of betaxolol may occur in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data with betaxolol reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Effects in non-clinical reproductive toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

In oral reproductive toxicity studies, RS-(±)-betaxolol and S-(-)-betaxolol were not teratogenic in rats and rabbits. However in rat embryo-fetal development (EFD) studies, embryonal mortality was observed at maternal toxic doses of 400 mg/kg/day. In rabbit EFD studies embryo-fetal toxicity, post-implantation loss and abortions were observed at doses of 12 mg/kg/day. Rabbit was the most sensitive species and the no-observed-adverse-effect-level (NOAEL) for developmental toxicity of S-(-)-Betaxolol was considered to be 4 mg/kg/day.

Maternal and F_1 developmental toxicity was observed following oral administration of 150 mg/kg/day Betaxolol (both S-betaxolol and RS-betaxolol). There were no adverse maternal effects and no developmental toxicity at 50 mg/kg/day.

A fertility study in rats showed abnormalities at the oral mid- and high- dose (32 and 256 mg/kg/day) groups. The observed abnormalities (decrease in the number of live fetuses per litter, post-implantation losses, neonatal mortality and decrease in the mean litter weight) reached statistical significance in the high-dose group. The development of the surviving offspring was normal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium chloride
Disodium edetate
Hydrochloric acid and/or sodium hydroxide (to adjust pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Discard four weeks after first opening.

6.4 Special precautions for storage

Keep the dropper container in the outer carton in order to protect from light. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml dropper container.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Novartis Pharma NV
Medialaan 40
B-1800 Vilvoorde

8. MARKETING AUTHORISATION NUMBER

BE133077

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 February 1985.
Date of latest renewal: 25 April 2005.

10. DATE OF REVISION OF THE TEXT

Date of approval of the text: 01/2019