Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Moxivig 0.5% w/v eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin (0.5% w/v).
Each eye drop contains 190 micrograms of moxifloxacin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution

Clear, greenish−yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Topical treatment of purulent bacterial conjunctivitis, caused by moxifloxacin susceptible strains (see sections 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

For ocular use only. Not for injection. MOXIVIG 0.5%w/v eye drops, solution should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

Use in adults including the elderly (≥ 65 years)
The dose is one drop in the affected eye(s) 3 times a day.
The infection normally improves within 5 days and treatment should then be continued for a further 2−3 days. If no improvement is observed within 5 days of initiating therapy, the diagnosis and/or treatment should be reconsidered. The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection.

Paediatric patients
No dosage adjustment is necessary.

Use in hepatic and renal impairment
No dosage adjustment is necessary.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

In order to prevent the drops from being absorbed via the nasal mucosa, particularly in new-born infants or children, the nasolacrimal ducts should be held closed for 2 to 3 minutes with the fingers after administering the drops. After cap is removed, if tamper evident snap collar is loose, remove before using the product.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching (see section 4.8).

If an allergic reaction to MOXIVIG occurs, discontinue use of the medicinal product. Serious acute hypersensitivity reactions to moxifloxacin or any other product ingredient may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.

As with other anti−infectives, prolonged use may result in overgrowth of non−susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in older patients and those treated concurrently with corticosteroids. Following ophthalmic administration of MOXIVIG plasma concentrations of moxifloxacin are much lower than after therapeutic oral doses of moxifloxacin (see section 4.5 and 5.2), however , caution should be exercised and treatment with MOXIVIG should be discontinued at the first sign of tendon inflammation (see section 4.8).

Data are very limited to establish efficacy and safety of MOXIVIG in the treatment of conjunctivitis in neonates. Therefore use of this medicinal product to treat conjunctivitis in neonates is not recommended.

MOXIVIG should not be used for the prophylaxis or empiric treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum, because of the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae*. Patients with eye infections caused by *Neisseria gonorrhoeae* should receive appropriate systemic treatment.

The medicinal product is not recommended for the treatment of *Chlamydia trachomatis* in patients less than 2 years of age as it has not been evaluated in such patients. Patients older than 2 years of age with eye infections caused by *Chlamydia trachomitis* should receive appropriate systemic treatment.

Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomitis* or *Neisseria gonorrhoeae*.

Patients should be advised not to wear contact lenses if they have signs and symptoms of a bacterial ocular infection.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with MOXIVIG 0.5% w/v Eye Drops, Solution. Given the low systemic concentration of moxifloxacin following topical ocular administration of the medicinal product (see Section 5.2), drug interactions are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of MOXIVIG in pregnant women. However, no effects on pregnancy are anticipated since the systemic exposure to moxifloxacin is negligible. The medicinal product can be used during pregnancy.

Breastfeeding
It is unknown whether moxifloxacin/metabolites are excreted in human milk. Animal studies have shown excretion of low levels in breast milk after oral administration of moxifloxacin. However, at therapeutic doses of MOXIVIG no effects on the suckling child are anticipated. The medicinal product can be used during breast-feeding.

Fertility
Studies have not been performed to evaluate the effect of ocular administration of MOXIVIG on fertility.

4.7 Effects on ability to drive and use machines

MOXIVIG 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 should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2,252 patients, MOXIVIG was administered up to 8 times a day, with over 1,900 of these patients receiving treatment 3 times daily. The overall safety population that received the medicinal product consisted of 1,389 patients from the United States and Canada, 586 patients from Japan and 277 patients from India. No serious ophthalmic or systemic undesirable effects related to the medicinal product were reported in any of the clinical studies. The most frequently reported treatment-related undesirable effects with the medicinal product were eye irritation and eye pain, occurring at an overall incidence of 1 to 2%. These reactions were mild in 96% of those patients who experienced them, with only 1 patient discontinuing therapy as a result.

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, undesirable effects are presented in decreasing order of seriousness.

System Organ Classification	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Rare	haemoglobin decreased
Immune system disorders	Not known	hypersensitivity
Nervous system disorders	Uncommon	headache
	Rare	paresthesia
	Not known	dizziness
Eye disorders	Common	eye pain, eye irritation
	Uncommon	punctate keratitis, dry eye, conjunctival haemorrhage, ocular hyperaemia, eye pruritus, eyelid oedema, ocular discomfort,
	Rare	corneal epithelium defect, corneal disorder, conjunctivitis, blepharitis, eye swelling, conjunctival oedema, vision blurred, visual acuity reduced, asthenopia, erythema of eyelid
	Not known	endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, intraocular pressure increased, corneal opacity, corneal infiltrates, corneal deposits,

		eye allergy, keratitis, corneal oedema, photophobia, , eyelid oedema, lacrimation increased, eye discharge, foreign body sensation in eyes
Cardiac disorders	Not known	palpitations
Respiratory, thoracic and mediastinal disorders	Rare Not known	nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat) dyspnoea
Gastrointestional disorders	Uncommon Rare Not known	dysgeusia vomiting nausea
Hepatobiliary disorders	Rare	alanine aminotransferase increased, gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Not known	erythema, rash, pruritus, urticaria

Description of selected adverse reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria and itching (see section 4.4).

Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

Paediatric population

In clinical trials, MOXIVIG has shown to be safe in paediatric patients, including neonates. In patients under 18 years old, the two most frequent adverse reactions were eye irritation and eye pain, both occurring at an incidence rate of 0.9%.

Based on data from clinical trials involving paediatric patients, including neonates (see section 5.1), the type and severity of adverse reactions in the paediatric population are similar to those in adults.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of the medicinal product.

The total amount of moxifloxacin in a single container is too small to induce adverse effects after accidental ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; anti−infectives, other anti-infectives, ATC code: S01A E07

Mode of Action:
Moxifloxacin, a fourth-generation fluoroquinolone, inhibits the DNA gyrase and topoisomerase IV required for bacterial DNA replication, repair, and recombination.

Resistance:
Resistance to fluoroquinolones, including moxifloxacin generally occurs by chromosomal mutations in genes encoding DNA gyrase and topoisomerase IV. In Gram-negative bacteria, moxifloxacin resistance can be due to mutations in *mar* (multiple antibiotic resistance) and the *qnr* (quinolone resistance) gene systems. Resistance is also associated with expression of bacteria efflux
proteins and inactivating enzymes. Cross-resistance with beta-lactams, macrolides and aminoglycosides is not expected due to differences in mode of action.

Susceptibility Testing Breakpoints
There are no pharmacological data correlated with clinical outcome for moxifloxacin administered as a topical agent. As a result, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) suggests the following epidemiological cut-off values (ECOFF mg/l) derived from MIC distribution curves to indicate susceptibility to topical moxifloxacin:

Corynebacterium	ND
Staphylococcus aureus	0.25 mg/l
Staphylococcus, coag-neg.	0.25 mg/l
Streptococcus pneumonia	0.5 mg/l
Streptococcus pyogenes	0.5 mg/l
Streptococcus, viridans group	0.5 mg/l
Enterobacter spp.	0.25 mg/l
Haemophilus influenza	0.125 mg/l
Klebsiella spp.	0.25 mg/l
Moraxella catarrhalis	0.25 mg/l
Morganella morganii	0.25 mg/l
Neisseria gonorrhoeae	0.032 mg/l
Pseudomonas aeruginosa	4 mg/l
Serratia marcescens	1 mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of moxifloxacin in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram−positive micro−organisms:
Corynebacterium species including *Corynebacterium diphtheriae* *Staphylococcus aureus (methicillin susceptible)* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Streptococcus viridans Group*

Aerobic Gram−negative micro−organisms*:*
Enterobacter cloacae *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Serratia marcescens*
Anaerobic micro-organisms:
Proprionibacterium acnes
Other micro−organisms:
Chlamydia trachomatis
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram−positive micro−organisms:
Staphylococcus aureus (methicillin resistant) *Staphylococcus, coagulase-negative species (methicillin resistant)*
Aerobic Gram−negative micro−organisms*:*
Neisseria gonorrhoeae
Other micro−organisms:
None
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram−negative micro−organisms*:*
Pseudomonas aeruginosa
Other micro−organisms:
None

5.2 Pharmacokinetic properties

Following topical ocular administration of MOXIVIG, moxifloxacin was absorbed into the systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who received bilateral topical ocular doses of the medicinal product 3 times a day for 4 days. The mean steady−state C_{max} and AUC were 2.7 ng/ml and 41.9 ng·hr/ml, respectively.
These exposure values are approximately 1,600 and 1,200 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half−life of moxifloxacin was estimated to be 13 hours.

5.3 Preclinical safety data

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

As with other quinolones, moxifloxacin was also genotoxic *in vitro* in bacteria and mammalian cells. As these effects can be traced to the interaction with bacterial gyrase and in considerably higher concentrations to the interaction with topoisomerase II in mammalian cells, a threshold level for genotoxicity can be assumed. In *in vivo* tests, no evidence of genotoxicity was found, despite high doses of moxifloxacin. The therapeutic doses for human use therefore provide adequate safety margin. No indication of a carcinogenic effect was observed in an initiation promotion model in rats.

Unlike other quinolones, moxifloxacin showed no phototoxic or photogenotoxic properties in extensive *in vitro* and *in vivo* studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Discard 4 weeks after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 ml bottle with DROP−TAINER dispensing system consisting of a transparent low density polyethylene bottle and dispensing plug and white polypropylene closure. Tamper evidence is provided by a security seal around the closure of the bottle.

Pack size: box containing 1 bottle

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Ltd
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Camberley
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0013/132/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 31st May 2014

10 DATE OF REVISION OF THE TEXT

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