SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ducressa 1 mg/ml + 5 mg/ml, eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of eye drops, solution, contains dexamethasone sodium phosphate equivalent to 1 mg of dexamethasone and levofloxacin hemihydrate equivalent to 5 mg of levofloxacin.

One drop (about 30 microliter) contains about 0.03 mg of dexamethasone and 0.150 mg of levofloxacin.

Excipient(s) with known effect:

One ml of eye drops solution contains 0.05 mg benzalkonium chloride and one drop contains about 0.0015 mg of benzalkonium chloride.

One ml of eye drops solution contains 4.01 mg phosphates and one drop contains 0.12 mg phosphates.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops).
A clear, greenish-yellow solution practically free from particles with a pH of 7.0-7.4 and osmolality of
270-330 mOsm/Kg. The expelled drops appear clear and colorless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ducressa eye drops solution is indicated for prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

One drop instilled into the conjunctival sac after surgery every 6 hours.
Duration of treatment is 7 days. Care should be taken not to discontinue therapy prematurely.
If one dose is missed, treatment should continue with the next dose as planned.
Re-evaluation of the patient to assess the need to continue the administration of corticosteroid eye drops as monotherapy is recommended after the completion of one week of therapy with Ducressa eye drops. The length of this treatment can depend on the patient's risk factors and outcome of surgery and must be determined by the doctor according to slit-lamp microscopic findings and depending on the severity of the clinical picture. A follow-up treatment with steroid eye drops should not normally exceed 2 weeks. However, care should be taken not to discontinue therapy prematurely.

Paediatric population

The safety and efficacy of Ducressa in children and adolescents below the age of 18 years have not been established. No data are available.
Ducressa is not recommended for use in children and adolescents below the age of 18 years.
Elderly patients

No dosage adjustment in elderly patients is necessary.

Use in renal/hepatic impairment

Ducressa has not been studied in patients with renal/hepatic impairment and Ducressa should therefore be used with caution in such patients.
Method of

administration

Ocular use.

One drop should be administered in the lateral canthus while applying pressure at the medial canthus to prevent drainage of the drops.
Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.
Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.
Nasolacrimal occlusion by compression of lacrimal ducts may reduce systemic absorption.
In case of concomitant treatment with other eye drops solutions, instillations should be spaced out by 15 minutes.

4.3 Contraindications

- Hypersensitivity to active substance levofloxacin or to other quinolones, to dexamethasone, or to other steroids, or to any of the excipients listed in section 6.1;
- Herpes simplex keratitis, varicella and other viral disease of the cornea and conjunctiva;
- Mycobacterial infections of the eye caused by, but not limited to, acid-fast bacilli such as Mycobacterium tuberculosis, Mycobacterium leprae, or Mycobacterium avium;
- Fungal diseases of ocular structures;
- Untreated purulent infection of the eye.

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4.4 Special warnings and precautions for use

Ocular effects

Ducressa is for ocular use only. Ducressa must not be injected sub-conjunctively. The solution should not be introduced directly into the anterior chamber of the eye.

Prolonged use may induce antibiotic resistance with result of overgrowth of non-susceptible organisms, including fungi. If infection develops, the treatment should be discontinued and alternative therapy used. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension/glaucoma but this is unlikely when Ducressa is used for the recommended treatment period (7 days). In any case, it is advisable that the intraocular pressure be checked frequently. The risk of corticosteroid-induced increase in the intraocular pressure is increased in predisposed patients (e.g. diabetes).

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may be related to complications to cataract surgery, development of glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Topical ophthalmic corticosteroids may slow corneal wound healing. Topical ocular NSAIDs are also known to slow or delay healing. Concomitant use of topical ocular NSAIDs and steroids may increase the potential for healing problems.

In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.

Systemic effects

Fluoroquinolones have been associated with hypersensitivity reactions, even following a single dose. If an allergic reaction to levofloxacin occurs, discontinue the medication.
Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including levofloxacin, particularly in older patients and those treated concurrently with corticosteroids. Therefore, caution should be exercised and treatment with Ducressa should be discontinued at the first sign of tendon inflammation (see section 4.8).
Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, treatment should be progressively discontinued.

Effects on Immune System

Prolonged use (generally observed within 2 weeks of treatment) may also result in secondary ocular infections (bacterial, viral, or fungal) due to suppression of host response or to the delay of their healing. In addition, topical ocular corticosteroids may promote, aggravate or mask signs and symptoms of eye infections caused by opportunistic microorganisms. Occurrence of these conditions is limited in case of short term corticosteroid treatment such as the one suggested for Ducressa. *Excipients*

Benzalkonium chloride

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.
After cataract surgery patients should not wear contact lenses for the whole duration of therapy with Ducressa.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Since maximum plasma concentrations of levofloxacin and dexamethasone after ocular administration are at least 1000 times lower than those reported after standard oral doses, interactions with other products for systemic use are unlikely to be clinically relevant.
The concomitant use of probenecid, cimetidine, or ciclosporin with levofloxacin altered some pharmacokinetic parameters of levofloxacin, but not to a clinically significant extent.
Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.
CYP3A4 inhibitors (including ritonavir and cobicistat) may decrease dexamethasone clearance resulting in increased effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic

corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of dexamethasone and levofloxacin in pregnant women. Corticosteroids cross the placenta. Prolonged or repeated corticosteroid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation, lower birth weight and risk for high blood pressure, vascular disorders and insulin resistance in the adulthood. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. Studies in animals with corticosteroids have shown reproductive toxicity and teratogenic effects (including cleft palate; see section 5.3).

Since a relevant systemic corticosteroid exposure cannot be excluded after ocular administration, treatment with Ducressa is not recommended during pregnancy, and especially during the first three months, should only take place after a careful benefit-risk assessment.

Breastfeeding

Systemic corticosteroids and levofloxacin are excreted into human milk. No data are available, to indicate whether relevant amounts of dexamethasone are transferred into human breast milk and which are capable of producing clinical effects in the infant. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ducressa therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Systemically administered corticosteroids may impair male and female fertility by influencing hormonal secretion of the hypothalamus and pituitary gland as well as gametogenesis in testes and ovaries. It is unknown if dexamethasone impairs human fertility after ocular use.

Levofloxacin caused no impairment of fertility in rats at exposures considerably in excess of the maximum human exposure after ocular administration.

4.7 Effects on ability to drive and use machines

As with any eye drops, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies, 438 patients have been treated with Ducressa. No serious adverse reactions occurred. The most commonly reported non-serious adverse reactions are eye irritation, ocular hypertension and headache.

Tabulated list of adverse reactions

The following adverse reactions have been reported with Ducressa during clinical trials that enrolled patients after cataract surgery (within each frequency grouping, adverse reactions are presented in order of decreasing frequency).

The frequency of possible adverse reactions listed below is defined using 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
not known	Frequency cannot be estimated from the available data

Ducressa (levofloxacin/dexamethasone combination)

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Uncommon	Headache, dysgeusia.
Eye disorders	Uncommon	Eye irritation, abnormal sensation in eye, ocular hypertension.
Skin and subcutaneous tissue disorders	Uncommon	Pruritus.
Investigations	Uncommon	Intraocular pressure increased (*).
(*) > 6 mmHg that means significant intraocular pressure increase		

Adverse reactions that have been seen with either of the ophthalmic active substances (levofloxacin or dexamethasone), and may potentially occur also with Ducressa are listed below:

Levofloxacin

System Organ Class	Frequency	Adverse reactions
Immune system disorders	Rare	Extra-ocular allergic reactions, including skin rash.

	Very rare	Anaphylaxis.
Nervous system disorders	Uncommon	Headache.
Eye disorders	Common	Ocular burning, decreased vision and mucous strand.
	Uncommon	Lid matting, chemosis, conjunctival papillary reaction, lid oedema, ocular discomfort, ocular itching, ocular pain, conjunctival hyperaemia, conjunctival follicles, ocular dryness, lid erythema, and photophobia.
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis.
	Very rare	Laryngeal oedema.

Dexamethasone

System Organ Class	**Frequency**	**Adverse reactions**
Eye disorders	Very common	Increase of the intraocular pressure.*
	Common	Discomfort*, irritation*, burning*, stinging*, itching* and blurred vision.*
	Uncommon	Allergic and hypersensitivity reactions, delayed wound healing, posterior capsular cataract*, opportunistic infections, glaucoma.*
	Very rare	Conjunctivitis, mydriasis, ptosis, corticosteroid-induced uveitis, corneal calcifications, crystalline keratopathy, changes in corneal thickness*, corneal oedema, corneal ulceration and corneal perforation.
Skin and subcutaneous tissue disorders	Very rare	Face oedema.
Endocrine disorders	Not known	Cushing's syndrome, adrenal suppression.
* see section Description of selected adverse reactions		

Description of selected adverse reactions

Increase of intraocular pressure

Increase of the intra-ocular pressure (IOP) and glaucoma may occur. Prolonged use of corticosteroid treatment may result in ocular hypertension/glaucoma (especially for patients with previous high IOP induced by steroids or with pre-existing high IOP or glaucoma). Children and elderly patients may be particularly susceptible to steroid-

induced IOP rise (see section 4.4). Diabetics are also more prone to develop subcapsular cataracts following prolonged topical steroid administration.

Post procedural adverse reactions

Ocular disorders (e.g. corneal oedema, eye irritation, abnormal sensation in the eye, lacrimation increased, asthenopia, corneal disorder, dry eye, eye pain, ocular discomfort, uveitis, blurred vision, visual brightness, conjunctivitis) and nausea have been reported during clinical trials. These reactions are usually mild and transient and are assessed to be related to the cataract surgery itself.

Possible adverse reactions related to cornea

In diseases causing thinning of the cornea, topical use of steroids could lead to cornea perforation in some cases (see section 4.4).
Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Additional adverse reactions that have been observed with prolonged use of the active substance levofloxacin and may potentially occur also with Ducressa

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).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The total amount of levofloxacin and dexamethasone 21-Phosphate in vial of Ducressa is too small to induce toxic effects after an accidental intake.

In the case of topical overdose, the treatment should be stopped. In case of prolonged irritation, the eye(s) should be rinsed with sterile water.
The symptomatology due to accidental ingestion is not known. The physician may consider gastric lavage or emesis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination.

ATC code: S01C A01

Ducressa is a fixed dose combination of two active substances: levofloxacin and dexamethasone.

Levofloxacin:

Mechanism of action:

Levofloxacin, the active L-isomer of ofloxacin, is a fluoroquinolone antibacterial agent, that inhibits bacterial type II topoisomerases—DNA gyrase and topoisomerase IV. Levofloxacin preferentially targets DNA gyrase in Gram negative bacteria and topoisomerase IV in Gram positive bacteria. The spectrum of activity against ocular pathogens includes aerobic Gram-positive microorganisms (e.g. *S. aureus* MSSA, *S. pyogenes, S. pneumoniae*, viridans group streptococci), aerobic Gram-negative bacteria (e.g. *E. coli, H. influenzae, M. catarrhalis, P. aeruginosa* community isolates), other organisms (e.g. *Chlamydia trachomatis*).

Mechanisms of resistance

Bacterial resistance to levofloxacin can develop primarily due to two main mechanisms, namely a decrease in the intrabacterial concentration of a drug, or alterations in a drug's target enzymes. Target site alteration results from mutations in the chromosomal genes encoding the DNA gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE; grlA and grlB in Staphylococcus aureus). Resistance due to low intrabacterial drug concentration follows either from altered outer-membrane porins (OmpF) leading to reduced entry of fluoroquinolones in Gram-negative bacteria or from efflux pumps. Efflux-mediated resistance has been described in pneumococci (PmrA), staphylococci (NorA), anaerobes, and Gram negative bacteria. Finally, plasmid-mediated resistance to quinolones (determined by the qnr gene) has been reported in *Klebsiella pneumoniae and in E.coli*.

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Cross-resistance

Cross-resistance between fluoroquinolones may occur. Single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the fluoroquinolone class. Altered outer-membrane porins and efflux systems may have a broad substrate specificity, targeting several classes of antibacterial agents and leading to multiresistance.

Susceptibility testing interpretive criteria

There are no interpretive criteria.

Dexamethasone:

Mechanism of action:

Corticosteroids like dexamethasone suppress vascular endothelial cell adhesion molecules, cyclooxygenase I or II, and cytokine expression. This action culminates in a reduced expression of proinflammatory mediators and the suppression of adhesion of circulating leukocytes to the vascular endothelium, thereby preventing their migration into inflamed ocular tissue. Dexamethasone has marked anti-inflammatory activity with reduced mineralocorticoid activity compared with some other steroids and is one of the most potent anti-inflammatory agents.

Clinical efficacy:

The efficacy of Ducressa has been investigated in a controlled study to evaluate the non-inferiority of the Ducressa vs. a standard treatment with a commercial formulation of tobramycin (0.3%) and dexamethasone (0.1%) eye drops for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults. The Investigator in charge of evaluating study parameters was blinded to treatment assignment. Patients who completed their cataract surgery without complications were assigned to Ducressa eye drops, 1 drop 4 times a day for 7 days, followed by dexamethasone 0.1% eye drops, 1 drop 4 times a day, for an additional 7 days, or to reference tobramycin + dexamethasone eye drops, 1 drop 4 times a day for 14 days.

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Data of efficacy were available in 395 patients given Ducressa and in 393 patients given the reference product after cataract surgery. After 14 days of treatment, the proportion of patients with no signs of inflammation (primary endpoint of the study) in the Ducressa followed by dexamethasone group compared to the tobramycin + dexamethasone group was 95.19% vs. 94.91%, respectively. The difference between the two proportions was 0.0028 (95% CI: [-0.0275; 0.0331]), which demonstrated the non-inferiority of the test vs. reference treatment regimen. No occurrence of endophthalmitis was reported during the study for either group. Signs of anterior chamber inflammation were absent in Ducressa arm in 73.16% at day 4 and in 85.57% of patients at day 8 after surgery. In tobramycin + dexamethasone arm, signs of anterior chamber inflammation were absent in 76.84% at day 4 and in 86.77% of patients at day 8. Conjunctival hyperemia was already absent at day 4 in 85.75% in Ducressa treatment arm vs. 82.19% in tobramycin + dexamethasone arm, respectively. The safety profile was similar in both groups

Pediatric population

The Regulator has waived the obligation to submit the results of studies with Ducressa in all subsets of the paediatric population for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery (see section 4.2 for information on pediatric use).

5.2 Pharmacokinetic properties

The ocular instillation of Ducressa results in absorption of both actives to the ocular tissues and, at a much lower extent, to the systemic circulation. After instillation to rabbit eyes, the plasma concentrations of levofloxacin increase with the dose after both single and repeated administration. Low levels of dexamethasone sodium phosphate are measured in plasma. In fact, dexamethasone sodium phosphate is rapidly metabolised *in vivo* to dexamethasone, which is the active metabolite. Dexamethasone exposure

increases with the dose and after repeated doses a minor accumulation of both levofloxacin and dexamethasone is evident. Both levofloxacin and dexamethasone levels in ocular tissues (aqueous humour, cornea and conjunctiva) result to be higher than the maximum plasma levels after single and repeated doses. In particular, after 28-day treatment levofloxacin and dexamethasone levels in ocular tissues are 50 to 100-fold and 3 to 4-fold higher than the Cmax in plasma, respectively.
One-hundred-twenty-five patients undergoing cataract surgery have been randomized to 3 groups: levofloxacin, dexamethasone and Ducressa. One drop of each drug was administered 90 and 60 minutes before limbal paracentesis. The mean of the observed values for the concentration of levofloxacin was equal to 711.899 ng/mL (95% CI: 595.538; 828.260) in the Ducressa group compared to 777.307 ng/mL (95% CI: 617.220; 937.394) when levofloxacin was administered alone. The concentrations of levofloxacin in the aqueous humour are well above the minimum inhibitory concentrations for the ocular pathogens in levofloxacin's spectrum of activity.
When Ducressa was administered dexamethasone reached an aqueous humour concentration of 11.774 ng/mL (95% CI: 9.812; 13.736) compared to 16.483 ng/mL (95% CI: 13.736; 18.838) when dexamethasone was administered alone.

Both levofloxacin and dexamethasone are eliminated via urine.

5.3 Preclinical safety data

Repeated-dose ocular toxicity studies with the levofloxacin/dexamethasone fixed dose combination for up to 28 days in rabbits revealed systemic toxicities attributable to exaggerated pharmacological effects of dexamethasone (focal tubular cell necrosis and glomerulopathy with necrosis and/or hyaline depositions in kidneys, hepatic hypertrophy with intracellular hyaline inclusions and single cell necrosis, atrophy of adrenal gland cortex and lymphocyte decreases due to atrophy of spleen, thymus and lymph nodes). Such effects were observed only at about 3-fold higher exposures than achieved at the maximum recommended human ocular dose, indicating little relevance to clinical use.
Gyrase inhibitors have been shown to cause growth disorders of weight bearing joints in animal studies. In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs after high oral doses.
<u>Genotoxicity and carcinogenicity</u>

Dexamethasone and levofloxacin did not reveal any clinically relevant genotoxic or carcinogenic potential.
<u>Reproductive toxicity:</u>

Levofloxacin did not influence fertility and only impaired embryo-foetal development in animals at exposures, considerably in excess of those

achievable at the recommended ocular therapeutic dose in humans. Topical and systemic administration of dexamethasone impaired male and female fertility and induced teratogenic effects including formation of cleft palate, intra-uterine growth retardation and foetal mortality. Peri- and postnatal toxicity of dexamethasone was also observed.
Phototoxic potential:

Studies in the mouse after both oral and intravenous dosing showed levofloxacin to have phototoxic activity only at very high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate monohydrate
Disodium phosphate dodecahydrate
Sodium citrate
Benzalkonium chloride
Sodium hydroxide /Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3years.
Discard within 28 days 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 Low-Density Polyethylene (LDPE) bottle, with a LDPE dropper tip and a High-Density Polyethylene (HDPE) screw cap.
Pack sizes: 1 bottle x 5 ml

6.6 Special precautions for disposal

Any unused antibiotic or antibiotic residual solution as well as materials that have been used for administration should be disposed in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

8 MARKETING AUTHORISATION NUMBER(S)

PL 16058/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/09/2021

10 DATE OF REVISION OF THE TEXT

20/10/2022