

Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Dubine 10 mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains 10 mg of ozenoxacin

Excipient(s) with known effect:

Each gram of cream contains 1mg of benzoic acid (E-210), 150 mg of propylene glycol and 40 mg of stearyl alcohol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.

Pale yellow, homogeneous cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dubine is indicated for the short term treatment of non-bullous impetigo in adults, adolescents, children, and infants aged 6 months and older) (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial medicinal products.

4.2 Posology and method of administration

Adults, adolescents, children, and infants aged 6 months and older

A thin layer of cream should be applied to the affected area twice daily for five days. The treated area may be covered by a sterile bandage or gauze dressing, if desired.

Patients not showing a clinical response within three days should be re-evaluated and alternative therapy should be considered.

Special populations

Elderly

No dosage adjustment is necessary.

Renal impairment

No dosage adjustment is necessary. See section 5.2.

Hepatic impairment

No dosage adjustment is necessary. See section 5.2.

Paediatric population

The safety and efficacy of ozenoxacin 10 mg/g cream in children under 6 months of age have not been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Ozenoxacin is for cutaneous use only.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Treatment of bullous impetigo with ozenoxacin is not recommended (see section 5.1).

Safety and efficacy have not been established in the following:

- Bullous impetigo
- Impetigo lesions exceeding 100 cm² in total surface area in adults and adolescents
- Impetigo lesions exceeding 100 cm² in total surface area or exceeding 2% of the body surface area in children less than 12 years of age

The efficacy of ozenoxacin in the treatment of impetigo in patients with pre-existing skin conditions has not been evaluated in clinical studies.

Sensitisation or severe local irritation

In the event of a sensitisation or severe local irritation from the use of ozenoxacin cream, treatment should be discontinued, the cream carefully wiped off, and appropriate alternative therapy for the infection instituted.

Caution should be exercised when used on patients with increased skin sensitivity, e.g. rosacea or seborrhoeic dermatitis, since deterioration of already present skin conditions have been observed.

Eyes and mucous membranes

Ozenoxacin cream must be kept away from the eyes and mucous membranes.

Ingestion

Care must be taken to avoid ingestion which is especially important in children who has lesions around the mouth.

Dubine contains propylene glycol which may cause skin irritation.

Dubine contains stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

Dubine contains benzoic acid which may be irritant to the skin, eyes and mucous membranes and may increase the jaundice in pre-term and full-term jaundiced neonates because of its absorption through the skin.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of concurrent application of ozenoxacin and other topical medicinal products to the same area of skin has not been studied, and it is not recommended.

In human liver microsomes, ozenoxacin showed to cause mild direct competitive inhibition of CYP3A4 at high concentrations (100µM), and possibly cause very mild time-dependent inhibition of CYP2C9 at high concentrations (200µM). However, since systemic exposure to ozenoxacin was not observed following topical application of 10 mg/g cream in adult and paediatric patients aged 6 months and older (see section 5.2), it is not expected that concurrent systemic administration of CYP3A4 or CYP2C9 substrates will result in clinically important inhibition of their metabolism by ozenoxacin.

Ozenoxacin does not induce cytochrome P450 enzymes in vitro.

In vitro data, very strongly suggest that the use of ozenoxacin in combination with commonly used antimicrobial agents should not represent a risk to clinical outcome.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of ozenoxacin in pregnant women. Studies in animals have shown reproductive toxicity after oral exposure (see section 5.3).

No effects during pregnancy are anticipated, since systemic exposure to ozenoxacin is negligible.
Dubine can be used during pregnancy.

Breast-feeding

It is unknown whether ozenoxacin is excreted in human breast milk. The excretion of ozenoxacin in milk has not been studied in animals. No effects on the breastfed infant are anticipated since the systemic exposure of the breast-feeding woman to ozenoxacin is negligible. Dubine cream can be used during breast-feeding. As a precaution, it is recommended to avoid applying Dubine cream to the breast area to protect the suckling infant from unintentional oral drug uptake.

Fertility

There are no data on the effects of ozenoxacin on human fertility. No treatment-related effects on male or female fertility have been shown in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Dubine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies in which 559 patients with superficial skin infections applied ozenoxacin cream, the most commonly reported adverse reaction was application site irritation, which affected less than 1% of patients.
No significant safety issues were reported during the clinical studies.

Tabulated list of adverse reactions

The following convention has been used for the classification of frequency: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

Organ systems	Uncommon
General disorders and administration site condition	Application site irritation
	Application site pruritus

Paediatric population

During the clinical development program no adverse drug reactions were reported in the paediatric population. Frequency, type and severity of adverse reactions in the paediatric population are expected to be the same as 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

Any sign or symptom of overdose, either topically or by accidental ingestion, should be treated symptomatically. No specific antidote is known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use, Antibiotics for topical use. ATC code: D06AX14

Mechanism of action

Ozenoxacin is a non-fluorinated quinolone with a dual inhibitory activity against bacterial DNA replication enzymes, DNA gyrase A and topoisomerase IV. This effect is mediated by the ability of quinolones to stabilize complexes of DNA and both DNA gyrase and topoisomerase IV thus, blocking progression of the replication fork.

The bactericidal activity of ozenoxacin has been demonstrated by the mean of kill curves experiments.

Mechanism of resistance

The development of quinolone resistance is caused by point mutations in discrete regions of the DNA gyrase (*gyrA*) and topoisomerase IV (*griA*) genes called the Quinolone Resistance-Determining Regions (QRDR).

Ozenoxacin shows a dual target of action, inhibiting DNA gyrase and topoisomerase IV, showing an ability to inhibit both enzymes. As a result of this inhibitory target activity and bactericidal property, ozenoxacin shows a low frequency of selection of spontaneous resistant mutants.

Against Gram-positive organisms Ozenoxacin has shown no cross-resistance with other families of commercial antibacterial, and retains activities below the breakpoints for mutants resistant to other marketed quinolones.

It is worth noting that ozenoxacin shows the same activity against methicillin-sensitive and methicillin-resistant strains of all studied bacterial species.

Pharmacodynamic effects

Antibacterial spectrum

Ozenoxacin is characterized by its potency and bactericidal activity against clinical bacterial isolates involved in skin infections, including *S. aureus* and *S. pyogenes*. The proposed epidemiological cut off (ECOFF) values for *S. aureus* and *S. pyogenes*, , are of 0.008 and 0.06 µg/ml, respectively. However, the differences in sensitivity to the product between populations are not always related to the clinical breakpoints and the therapeutic properties of the product. For this reason, EUCAST assumes that using ECOFF values might underestimate the activity of some agents in topical preparations.

Commonly susceptible species
<i>Staphylococcus aureus</i> ¹
<i>Streptococcus pyogenes</i> ¹
<i>Staphylococcus capitis</i> *
<i>Staphylococcus epidermidis</i> *
<i>Staphylococcus haemolyticus</i> *
<i>Staphylococcus lundunensis</i> *
<i>Staphylococcus warneii</i> *

<i>Streptococcus agalactiae</i> *
-
MR- <i>Staphylococcus aureus</i> (MRSA)* ²
MR- <i>Staphylococcus epidermidis</i> *
MR-coagulase-negative staphylococci (MR-CNS)*
MR- <i>Streptococcus pyogenes</i> *
MR- <i>Streptococcus agalactiae</i>

¹Activity has been satisfactorily demonstrated in clinical studies.

² *In vitro*, ozenoxacin was equally active against methicillinsusceptible and methicillinresistant strains of *S. aureus*. In clinical studies in all the cases the patients have achieved clinical improvement/cure.

* *In vitro*, ozenoxacin was shown to have a wide spectrum of bactericidal activity, especially against gram-positive bacteria. Ozenoxacin activity extends to strains of bacteria resistant to other antibiotics including mupirocin, quinolones and methicillin.

Clinical efficacy and safety

Two multicenter, randomized, blind clinical trials have been performed to compare the efficacy of ozenoxacin 10 mg/g cream to placebo for the treatment of impetigo in adult and paediatric population (one included retapamulin as an internal control).

	Total	Ozenoxacin	Placebo
N	723	361	362
0-6 months	4 (0.5%)	1(0.3%)	3 (0.8%)
6 months - <2 years	24 (3.3%)	11 (3.0%)	13 (3.6%)
2 years - <12 years	387 (53.5%)	196 (54.3%)	191 (52.8%)
12 years - <18 years	83 (11.5%)	42 (11.6%)	41 (11.3%)
≥ 18 years	225 (31.1%)	111 (30.7%)	114 (31.5%)

Clinical Response

	Ozenoxacin		Placebo	
	Study 1 (N= 155) n (%)	Study 2 (N= 206) n (%)	Study 1 (N= 156) n (%)	Study 2 (N= 206) n (%)
<i>Primary Efficacy Endpoint</i>				
Clinical Success at Visit 3 (day 6-7) ^a				
Clinical success	54 (34.8)	112 (54.4)	30 (19.2)	78 (37.9)
Clinical failure	98 (63.2)	91 (44.2)	120 (76.9)	121 (58.7)
Unable to determine	3	3	6	7

^a The difference in the success rates was very similar in both clinical trials (approximately 0.16) and statistically significant in both cases, confirming a greater clinical success in the ozenoxacin group than in the placebo group at end of therapy.

- The treatment comparison was done using only the outcomes of Clinical Success and Clinical Failure. Clinical improvement without complete success was considered as clinical failure.
- Further analyses were performed to evaluate the sensitivity where missing responses were imputed as clinical failures. The difference in the success rates was statistically significant (difference of 0.165; 95% CI 0.070 – 0.260; p<0.001).

The most commonly found pathogens were *Staphylococcus aureus* and *Streptococcus pyogenes*.
The microbiological success rate was also statistically significant superior for ozenoxacin versus placebo.

The number of patients with bullous impetigo included in ozenoxacin clinical trials was very limited. When the data from the two pivotal trials are pooled, a total of 56 subjects with bullous impetigo were included in the ozenoxacin

groups. The pooled clinical response rate in bullous impetigo was 30% (17/56 patients) in the ozenoxacin group and 32% (20/61) in the placebo group. The proportion of subjects in the ozenoxacin 1% cream group who achieved a clinical success in the bullous subgroup was very different among the two studies, 15.6% (5/32) (Study 1) and 50% (12/24) (Study 2), respectively.

Microbiological Response

	Ozenoxacin		Placebo	
	Study 1 (N= 154) n (%)	Study 2 (N= 125) n (%)	Study 1 (N= 152) n (%)	Study 2 (N= 119) n (%)
Bacteriological Success (%) at Visit 2 (Day 3-4)				
Microbiological success	109 (70.8)	109 (87.2)	58 (38.2)	76 (63.9)
Microbiological failure	37 (24)	16 (12.8)	90 (59.2)	32 (26.9)
Unable to determine	8	0	4	11
Bacteriological Success (%) at Visit 3 (End of Therapy, Day 6-7)				
Microbiological success	122 (79.2)	115 (92)	86 (56.6)	87 (73.1)
Microbiological failure	16 (10.4)	8 (6.4)	55 (36.2)	20 (16.8)
Unable to determine	16	2	11	12

Few *S. aureus* infections were resistant to methicillin, ciprofloxacin, mupirocin, fusidic acid, or retapamulin.

5.2 Pharmacokinetic properties

Absorption

No detectable systemic exposure levels were observed in adult healthy volunteers and in adult patients with impetigo following repeated topical application of ozenoxacin 10 mg/g cream for up to 7 days to intact and abraded skin.

Distribution

Plasma protein binding of [14C]-ozenoxacin was moderate (~80 to 85%) in human and dog plasma and did not appear to be dependent on concentration.

Biotransformation

Ozenoxacin was excreted mainly unchanged in animal studies (mini-pigs and rats).

Elimination

Since no detectable systemic exposure levels were observed in clinical studies, elimination has not been investigated in humans.

Special populations

No pharmacokinetic data are available in patients with renal or hepatic impairment. However, due to the undetectable systemic plasma levels that have been observed, no safety problems are foreseen.

Paedriatic population

No detectable systemic exposure levels were observed in any paediatric patient with impetigo (aged > 6 months of age) following topical administration of ozenoxacin 10 mg/g cream twice daily for 5 days, with the exception of one patient with blood samples that were very close to the limit of quantitation (0.5 ng/ml).

5.3 Preclinical safety data

Repeated dose studies

Topically administered, ozenoxacin was well tolerated. Plasma levels of ozenoxacin after single dermal administration were below LOQ while only low systemic exposure was detected after 28-day dermal administration.

Ozenoxacin was also well tolerated in both intact and abraded skin in minipigs after dermal administration during 28 consecutive days.

In the oral 28-day repeated dose toxicological studies in rats and dogs, where adequate systemic exposure was achieved, the NOAEL was 125 mg/kg/day and 50 mg/kg/day, respectively for each study. Since systemic exposure is negligible, no adverse effects are anticipated.

Genotoxicity

There was no evidence of mutagenicity/genotoxicity when evaluated in the required standard battery of genotoxicity testing for assessment of the genotoxic potential (Ames test, mouse lymphoma assay and in vivo rat micronucleus assay).

Reproductive toxicity

Systemic exposure to ozenoxacin at oral dosages up to 500 mg/kg/day in rats did not induce adverse effects on male or female fertility, parturition, lactation or maternal behavior on F0 generation and did not affect reproductive parameters and growth pattern on F1 generation where quantifiable levels of ozenoxacin in the pup plasma (F1 generation) on day 14 postpartum was demonstrated. In the rabbit, an increase in post-implantation loss and corresponding reduction in live fetuses per litter was observed at 40 mg/kg/day. Furthermore, in rat and rabbit at dosage up to 500 mg/kg/day and 40 mg/kg/day, respectively, during gestation period, a reduction in fetal body weights was observed, which in turn caused delays in skeletal development, but the product did not induce gross, visceral or skeletal fetal anomalies.

Juvenile animals

In the 2-weeks repeated oral toxicity study in juvenile dogs, where adequate systemic exposure was achieved, the NOAEL was 100 mg/kg/day.

There was no evidence of articular toxicity.

Local tolerance

Adverse effects usually related to quinolones, such as phototoxicity, photoallergenic and sensitizer potential have not been observed with ozenoxacin in the non-clinical studies conducted.

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that ozenoxacin may pose a risk to the aquatic environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol stearate
Ethylene glycol monopalmitostearate
Oleoyl macrogol glycerides
Octyldodecanol
Stearyl alcohol
Propylene glycol
Benzoic acid (E210)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened tube: 3 years

In-use stability after first opening: 45 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium tube with a white screw cap. The tube has an epoxy-phenolic internal lacquer and a sealant lacquer at the tube end.

Dubine is available in tubes containing 10 g of cream.

6.6 Special precautions for disposal

Once opened, the tube can be re-used for a second treatment, provided that 45 days of in-use shelf-life are not exceeded.

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

This medicinal product may pose a risk to the environment (see section 5.3).

7 MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028 – Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER

PA1744/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th June 2017

10 DATE OF REVISION OF THE TEXT

July 2018