

Public Assessment Report

Scientific discussion

**Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml,
ear drops, solution**

(ofloxacin)

NL/H/2980/001/DC

Date: 12 February 2015

This module reflects the scientific discussion for the approval of Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml, ear drops, solution. The procedure was finalised on 9 October 2014. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

ACMOM	Active chronic mucosal otitis media
AOM	Acute otitis media
BCF	Bioconcentration factor
CAS	Chemical abstracts service
CEP	Certificate of Suitability of the EP
CMR	Carcinogenic, mutagenic or toxic for reproduction
CMS	Concerned Member State
CSOM	Chronic suppurative otitis media
DT50	Degradation time for 50% of a compound
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ERP	European reference product
F _{pen}	Fraction of market penetration
INN	International nonproprietary name
kg	Kilogram
KNO	Nederlandse Vereniging voor KNO-heelkunde en Heelkunde van het Hoofd- Halsgebied
K _{ow}	Octanol-Water partition coefficient
LDPE	Low Density Polyethylene
LD50	Median Lethal Dose for 50% of population
MAH	Marketing authorisation holder
MEB	Medicines Evaluation Board
mg	milligram
ml	milliliter
mOsm	milliosmole
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin Resistant Staphylococcus Aureus
NHG	Nederlands Huisartsen Genootschap
NOEC	No observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent bioaccumulative toxicity
PEC	Predicted Environmental Concentration
Ph.Eur	European Pharmacopoeia
PL	Patient Leaflet
RH	Relative humidity
RMS	Reference Member State
SGOT	Serum-Glutamate-Oxaloacetate Transaminase
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UD	Unit Dose
UDS	Unscheduled DNA Synthesis
vPvB	Very persistent very bioaccumulating

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml, ear drops, solution, from Pharma Stulln GmbH.

The product is indicated for the treatment of:

- Chronic suppurative otitis media (CSOM) in adults and children over 12 years of age with perforated tympanic membranes.
- Acute otitis media (AOM) in pediatric patients over one year and older with tympanostomy tubes.

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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Oflocet 1.5 mg/0.5 ml, ear drops solution in single-dose container which has been registered in France by Sanofi Aventis since 1995 (original product). Oflocet is referred to as a European reference product (ERP), as ofloxacin containing ear drops for local use are not registered in the Netherlands (RMS) nor in the Concerned member state (CMS). However, eye drops containing ofloxacin have been registered in the Netherlands since 1990.

The CMS involved in this procedure was Austria.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. This is a hybrid application as bioequivalence cannot be demonstrated through bioavailability studies, due to the local action of this product.

II. QUALITY ASPECTS

II.1 Introduction

Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml is a clear, slightly greenish yellow solution, free from visible particles with pH 6.5–7.5 and osmolality of 260–330 mOsm/kg. It does not contain a preservative. Each unit dose container contains 1.5 mg ofloxacin in 0.5 ml of solution.

The ear drops are packed in 0.5 ml transparent LDPE unit dose containers. Strips of five unit dose containers are packed in laminated aluminum pouches.

The excipients are: sodium chloride, hydrochloric acid, sodium hydroxide, and water for injections.

II.2 Drug Substance

The active substance is ofloxacin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a pale yellow or bright yellow, crystalline powder, which is slightly soluble in water. Ofloxacin is a racemate, there is no polymorphism. As the drug substance is dissolved during manufacture of the drug product, potential polymorphism as well as the particle size of the drug substance does not need to be controlled.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification of the MAH is in accordance with the Ph.Eur. monograph on ofloxacin and the CEP and contains additional requirements for microbial contamination.

Batch analysis data on two commercial-scale batches are provided. Both batches demonstrated compliance with the drug substance specification of the MAH.

Stability of drug substance

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

Aim of the formulation development was the development of a generic of the reference product Oflocet ear drops, solution containing 1.5 mg ofloxacin/0.5 ml. The development of the product has been described. Excipients were chosen based on the reference product, review of the literature with regard to physicochemical characterisation of the drug substance and excipients used, and long-standing manufacturing experience. The qualitative composition of the generic product is identical to the reference product, except for the purified water, which has been replaced by water for injections. The drug product is isotonic and has a physiological pH. A commonly used manufacturing technique (blow-fill-seal) is applied.

An *in vitro* comparison was performed with one batch of the generic product and two batches of the reference product with regard to physicochemical properties and dosage. Comparison of physicochemical properties included pH, relative density, osmolality, ofloxacin content, sodium chloride content, and related substances.

With the exception of the pH and related substances, similar results were obtained. The pH of the generic product was 7.0 and of the reference product 6.5. However, according to literature the difference in pH is physiologically not relevant. Antibiotic ear drops of a neutral pH are well tolerated and are therefore preferred in case of middle ear infections with tympanic perforation. Therefore the levels of 7.0 as found give no indication for concern regarding auricular tolerability of this product versus the reference medicinal product.

For the reference medicinal product Oflocet ear drops the content of one single-dose container (0.5 ml) equals about 10 drops. A dose reproducibility study has been performed with the generic product. The content of one single-dose container (0.5 ml) equals about 17 drops, with an average drop size of 0.02872 ml, corresponding to 0.09 mg ofloxacin.

The generic and the reference product are regarded to be essentially similar from a chemical pharmaceutical point of view.

Overall, the pharmaceutical development has adequately been performed.

Manufacturing process

The manufacturing process involves dissolution of the drug substance and excipients in water for injections, sterilisation by filtration and aseptic filling using the blow-fill-seal technology. This is a common manufacturing process for ear drops packed in unit dose containers. Due to the use of LDPE as packaging material, terminal sterilization is not possible. Because an aseptic processing step is applied, the manufacturing process is considered (to be) non standard.

Process validation on three consecutive batches have been provided. The manufacturing process has been adequately validated.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Microbiological attributes

The drug product is sterile, in compliance with Ph. Eur. 2.6.1. The manufacturing process involves double sterile filtration followed by aseptic filling using the blow-fill-seal technology. Information about the filters is provided. Sterility is monitored in the stability studies.

Quality control of drug product

The product specification includes tests for appearance (clarity and opalescence, colour), identity of ofloxacin, relative density, pH, osmolality, assay of ofloxacin, purity, extractable volume, uniformity of dosage units, sterility, and particulate contamination (sub-visible particles). The release and shelf life specifications differ with regard to the limits for related substances.

The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three batches of the commercial batch size. All batches complied with the release specification.

Stability of drug product

Stability data have been provided for eight production scale batches. These were stored at 25°C/60% RH (five batches for 36 months, one batch for 9 months, and two batches for 6 months), 30°C/65% RH (five batches for 12 months), and 40°C/75% (six months). The conditions used in the stability studies are in accordance with the Guideline on stability testing (CPMP/QWP/122/02, rev 1 corr) regarding finished products packaged in semi-permeable containers. The containers were stored with and without laminated aluminum pouches. In the containers stored in pouches, increases were seen in the level of impurities. No out-of-specification results were observed. In the unpacked containers, out-of-specification results were observed for impurities, evaporative loss, and assay after six months at long term and accelerated storage conditions. Result of a photostability study under ICH conditions showed that the drug product is sensitive to light.

Based on the provided stability data, the claimed shelf life of 24 months for the drug product packed in the laminated aluminum pouches and the claimed shelf life of four weeks after opening of the pouches are acceptable. The proposed storage conditions "Do not store above 25°C. Do not refrigerate or freeze. Store in the original package in order to protect from light" are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

Pharmaceutical equivalence was sufficiently demonstrated for the relevant pharmaceutical properties by the results of the *in vitro* comparison, justifying a biowaiver for this locally active product on chemical-pharmaceutical grounds.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new non-clinical studies have been submitted for this application. The dossier consists of literature references, which are summarized below.

III.2 Pharmacology

Ofloxacin is a fluoroquinolone with broad antibacterial spectrum activity. Ofloxacin induces its antibacterial activity by inhibition of the enzyme DNA gyrase, the topoisomerase type II (also with part involvement of topoisomerase IV), which controls super coiling of DNA in bacteria for growth, where topoisomerase I unfolds the coiling. The topoisomerase II contains subunits A and B, and subunit A is the main target of fluoroquinolone antibiotics. Ofloxacin is active against most gram-negative bacteria *in vitro* and the gram-positive bacteria Staphylococci and Streptococci. Methicillin-resistant strains of Staphylococci (MRSA) may however be resistant to fluoroquinolones. Ofloxacin is also active against Chlamydia trachomatis and Mycoplasma pneumoniae.

The bacterial resistance to fluoroquinolones is developed via the *gyrA* mutation that codes for the A

subunit of the DNA gyrase enzyme. Resistance can occur through a multistep process. A single mutation can increase the minimum inhibitory concentration (MIC) slightly, and each subsequent mutation produces a progressively high level of resistance in a stepwise fashion. Unlike plasmid-mediated bacterial resistance (in *E. coli* and *Klebsiella*), in which resistance may disappear after removal of selective antibiotic pressure, the chromosomal (mutational) resistance is usually maintained in bacteria after discontinuation of the therapy and causes clinical problems. Resistance to ofloxacin can be produced *in vitro* in some strains of Enterobacteriaceae, *Pseudomonas aeruginosa* and Streptococci by serial passage in presence of increasing concentrations of the drug. Ofloxacin resistance resulting from spontaneous mutation occurs rarely *in vitro*. The potential for development of resistance to ofloxacin during ototopical administration might be less than that associated with systemic administration of the drug, because of the comparatively high drug concentration which is achieved in middle ear mucosa and surrounding tissues. Resistance to fluoroquinolones is often attributed by *E. coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and sometimes also by the methicillin-susceptible *Staphylococcus aureus*. Cross-resistance has been observed between ofloxacin and other fluoroquinolones and partial cross-resistance may be developed between ofloxacin and chemically distinct quinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has no demonstrable other pharmacological effects, especially after topical use in ear.

III.3 Pharmacokinetics

After oral administration, ofloxacin is rapidly and completely absorbed from the gastrointestinal tract and the bioavailability is 95 to 100%. Plasma half-life ranges from 5 to 8 hours. Ofloxacin is rapidly and widely distributed throughout the body including the body fluids, tissues and bones. About 25 to 30% of the drug bind to plasma proteins, mostly to albumin. The highest concentrations are found in the kidneys, gallbladder, liver, lungs, reproductive organs of male and female, phagocytic cells, urine, sputum, and the bile. Ofloxacin crosses the placenta and passes into breast milk. Serum concentrations following otic administration of 0.3% ofloxacin ear drops were around 4 – 5 ng/ml in adults with tympanostomy tubes and 10 ng/ml in case of perforated tympanic membranes. The concentration of drug in middle ear mucosa varied widely from 1.2 – 602 µg/g in 11 subjects. The ofloxacin concentration in otorrhea was high (389 – 2850 µg/g) following otic administration of 0.3% to 13 subjects with CSOM and perforated membranes. The average drug concentration in middle ear secretion, otorrhea, middle ear mucosa and in the surrounding tissues following otic instillation of ofloxacin 0.3% is estimated to be about 5 – 10 µg/g. Only a small part of the drug reaches the circulation. Following systemic absorption, only a small part of ofloxacin (<10%) is metabolised. 75 to 80% is excreted unchanged in the urine and 4 – 8% is found in the faeces.

III.4 Toxicology

Systemic use of fluoroquinolones at higher doses may induce gastrointestinal tract toxicity (nausea, vomiting and diarrhoea) and central nervous system effects (headache, dizziness, hallucination, delirium and seizures). Occasionally, fatal hypersensitivity has been observed also after otic use. Acute rhabdomyolysis has been documented in rare cases. Oral LD50 is reported as 1803 – 5450 mg/kg in mice, 1478 – 3750 mg/kg in rats, 200 mg/kg in dogs and 500 – 1000 mg/kg in monkeys. Intravenous LD50 is reported as 208 – 233 mg/kg in mice and 273 – 276 mg/kg in rats. Subcutaneous LD50 is reported as >10000 mg/kg in mice and 7070 – 9000 mg/kg in rats. In repeated dose studies in animals, toxic signs of oral or subcutaneous administration were found as hypoactivity, ptosis, dyspnoea, convulsion and tremor, and following intravenous injection, collapse, convulsion, dyspnoea irrespective of animal species. Additional signs were emesis frequently observed in dogs and monkeys. Additionally, in dogs, degenerative changes in the joints were seen following 4 weeks of oral administration, and, in young dogs, morphological changes in the testes. Additional effects following 4 weeks administration to rats were diarrhoea, decreased food consumption, increased water consumption, increased alkaline phosphatase activity and rarefaction of articular cartilage matrix. In chronic studies in rats, increased SGOT and serum alkaline phosphatase were observed as well as morphological changes in cartilage and an increase in incidence and severity of spontaneous lesions in the median femoral condyle. In immature rats treated orally for 21 days, ultrastructural changes were observed in the Achilles tendon.

Ofloxacin did not affect male or female fertility following oral administration up to 360 mg/kg/day to rats. Ofloxacin was not teratogenic in rats and rabbits at doses up to 11 or 4 times the human dose based on mg/m², respectively, but caused reduced birth weight and increased mortality in the pups and, in rats, skeletal variations. In rats dosed 5 times the human dose based on mg/m², no adverse effects were seen on late foetal development, labour, delivery, lactation, neonatal viability, or subsequent growth of the newborn.

Ofloxacin was not mutagenic in the Ames test, *in vitro* and *in vivo* cytogenic assay, sister chromatid exchange assay (Chinese hamster and human cell lines), unscheduled DNA synthesis, (UDS) assay using human fibroblasts, the dominant lethal assay, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocyte and in the mouse lymphoma assay. No carcinogenicity studies were performed with ofloxacin.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results Substance (INN/Invented Name): ofloxacin			
CAS-number (if available): 82419-36-1			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K _{ow}	OECD 107	log K _{ow} = -0.48	not PBT
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K _{ow}	-0.48	not B
	BCF	not assessed	
Persistence	DT50 or ready biodegradability	Not ready biodegradable	potentially P
Toxicity	NOEC or CMR	not assessed	potentially T
PBT-statement :		Ofloxacin is not considered PBT nor vPvB	
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default F _{pen}	0.03	µg/L	> 0.01 threshold
PEC _{surfacewater} , refined F _{pen}	0.009	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)	not assessed		

The action limits are not exceeded. Therefore a Phase II assessment is not necessary.

III.6 Discussion on the non-clinical aspects

This product is a hybrid formulation of Oflocet 1.5 mg/0.5 ml, ear drops solution in single-dose container which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The safety and efficacy of the well-known active substance ofloxacin (as ear drops) were already established for the innovator product Oflocet. However, since Oflocet was never authorized in the Netherlands and the CMS, the efficacy and safety of this hybrid product in the proposed indications were discussed in the context of this procedure.

The clinical overview is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Definitions and pathology

Acute otitis media (AOM) is an inflammation of the middle ear with accumulation of fluid in the middle ear and symptoms and signs of acute infection. *Acute otitis media (AOM)* is usually developing on the basis of a (viral) upper respiratory infection with blockage of the Eustachian tube and effusion in the middle ear, when the fluid in the middle ear gets additionally infected with bacteria. In most cases bacterial otitis media is a self-limiting disease.

Chronic suppurative otitis media (CSOM) (synonym active chronic mucosal otitis media (ACMOM)) is a chronic inflammation of the middle ear with a non-intact tympanic membrane, i.e., a perforation or tympanostomy tube, and otorrhea (ear discharge) for at least 2 weeks. This disease is much more common in persons with poor Eustachian tube function. Hearing impairment often accompanies this disease.

Therapeutic interventions

Tympanostomy tubes

The insertion of tympanostomy tubes in order to keep the middle ear aerated for a prolonged period of time, and to prevent the accumulation of fluid in the middle ear is the most performed surgical intervention.

Medicinal treatment

AOM is the most common reason for the use of antibiotics in children.

Prophylactic use of antibiotics in otitis media:

The prophylactic use of antibiotics in *acute otitis media* and *chronic suppurative otitis media* is not recommended. Beneficial effects are negligible and there is a risk of the development of resistance of pathogens

Therapeutic use of antibiotics in otitis media:

1st line healthcare primary care

In general practice in the Netherlands the initial approach is "watchful waiting using pain relieve medication" before proceeding to medical intervention (surgery or treatment with analgesics, decongestiva or antibiotics). If the use of antibiotics is considered the Dutch College of General Practitioners (NHG) recommends the following regimen:

First choice: amoxicillin, orally for 1 week; when amoxicillin is contraindicated: azithromycin for 3 days or cotrimoxazole for 5-7 days, orally.

2nd line healthcare

The Dutch Society of Otolaryngology–Head and Neck Surgery (KNO) recommends the following medicinal treatment in the case of *CSOM in children*:

- *Topical antibiotics*

First choice: ear drops containing non-quinolone antibiotic combinations (chloramphenicol or neomycin, oxytetracycline with polymyxin B, clioquinol, framycetin/gramicidin, colistin/bacitracin), usually combined with corticosteroids.

Only if these ear drops are not proven, effective treatment with quinolones (incl. ofloxacin) containing ear drops should be considered.

- *Oral antibiotics:*

If antibiotic ear drops and short courses of oral antibiotics appear to have no effect in children with CSOM, a 6-12 week course with co-trimoxazole (oral 2 of 18 mg/kg) can be considered.

Topical antibiotic containing products for use in the ear

In the Netherlands several antibiotic containing products for auricular use are registered.

All these products (except for Sofradex, ear drops) are indicated for the treatment of *otitis externa with an intact tympanic membrane*. Use in non-intact eardrums is contra-indicated, because of the potential risk of ototoxicity due to these products (for instance aminoglycosides like neomycin).

Sofradex ear drops (NL License RVG 04961) is the only topical antibiotic containing product, registered in NL that is indicated in ***otitis media***: "*Chronic recurrent otitis media with otorrhea, in the*

case of a sensitive micro-organism, in control of granulation tissue and the prevention of local inflammatory reactions.”.

Sofradex ear drops contain per ml: sodium metasulfobenzoate ester of dexamethasone, corresponding to 0.5 mg dexamethasone, 5 mg framycetin sulphate (= aminoglycoside) and 0.05 mg gramicidin (= bactericid cyclic polypeptide). Framycetin sulphate is an ototoxic ingredient/agent.

Although in practice ototoxicity with the use of short-course topical treatment with aminoglycoside containing ear drops is rare, alternative drugs that are not or less ototoxic (like the fluoroquinolones) are a addition to the currently available treatment options.

“Off label use” of ofloxacin containing eye drops in the ear

In the Netherlands ofloxacin 3 mg/mL containing **eye** drops were already used “off label” in **ear** infections like CSOM, *otitis media with tympanostomy tubes and otitis externa*.

The Dutch Paediatric formulary recommends the following posology of Trafloxal eye drops 3% in the ear:

Children aged < 12 years: 1-2 daily, 5 drops for a duration of 7-10 days

Children aged 12-18 years: 1-2 daily, 10 drops for a duration of 7-10 days

IV.2 Pharmacokinetics

Within the group of fluoroquinolones ofloxacin is comparable to ciprofloxacin and norfloxacin in pharmacokinetics. Newer quinolones such a levofloxacin and moxifloxacin have better tissue penetration. Bactericidal activity of fluoroquinolones depends on concentration of the antibiotic (i.e., the dose), more than the time above the minimum inhibitory concentration (MIC) that can be increased by the frequency of administration. Required MIC of 0.1 – 5 µg/ml is achieved with the topical application of Ofloxacin Stulln Unit Dose 1.5 mg/0.5 mL ear drops, solution.

Due to negligible plasma concentrations interactions of Ofloxacin 3 mg/mL with other agents following auricular use with the recommended doses are not expected.

Biowaiver

No comparative bioavailability studies have been conducted to support the application. Essential similarity with the originator product is based on comparative qualitative and physicochemical attributes of the product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/EWP/239/95) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. Since the quantitative composition of the active ingredient and the qualitative composition of the excipients of the product are similar to that of the reference product Oflocet 1.5 mg/0.5 ml ear drops, and the pharmaceutical properties (i.e. osmolarity, pH, relative density, drop size) are comparable to that of the reference product as well, a biowaiver can be granted. Ofloxacin Stulln Unit Dose 1.5 mg/ 0.5 ml ear drops, solution may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Pharmacodynamics

Mechanism of action

Ofloxacin, like other fluoroquinolones, interacts with the complexes of both DNA gyrase and DNA topoisomerase IV with DNA. Both enzymes are essential for DNA replication, and interaction of a quinolone with either enzyme-DNA complex traps the enzyme on DNA and creates a cleavable complex, which blocks bacterial DNA replication and can, under some conditions, generate double-strand breaks in DNA that are likely necessary for bactericidal activity.

Antibacterial spectrum

The antibacterial spectrum of ofloxacin comprises:

Aerobe, gram positive: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*. Methicillin-resistant strains of Staphylococci (MRSA) and *Enterococcus faecalis* may be resistant to fluoroquinolones.

Aerobe gram-negative: *Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, *Haemophilus influenza*, *Moraxella* spp., and frequently less active against *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Morganella morganii*, *Neisseria gonorrhoea*, *Pseudomonas* spp., *Serratia marcescens*.

Moreover, ofloxacin has antibacterial activity against Mycobacteria.

Bacterial resistance

The bacterial resistance to fluoroquinolones is developed via the gyrA mutation that codes for the A subunit of the DNA gyrase enzyme. Since the introduction of fluoroquinolones, the development of resistance to ofloxacin among Gram-positive bacteria has predominantly occurred in *MRSA* and *S. pneumoniae*. Obligate anaerobes are usually resistant. Cross-resistance has been observed between ofloxacin and other fluoroquinolones.

The potential for development of resistance to ofloxacin during ototopical administration might be however less than that associated with systemic administration of the drug, because of the comparatively high drug concentration that is achieved in middle ear mucosa and surrounding tissues after topical application of ofloxacin ear drops, solution.

IV.4 Clinical efficacy

In support of this hybrid application no additional clinical studies were performed by the MAH. The originator product is currently on the market in France (Oflocet 1.5 mg/0.5 ml = ERP), registered by Sanofi-Aventis France for the use in *AOM and CSOM with non-intact tympanic membranes*. In Portugal (Floxedol 3 mg/mL) and the USA (Floxin Otic 0.3%) the product is registered for *AOM, CSOM and otitis externa*.

Ofloxacin 0.3% ear drops, solutions have been tested in a number of open and comparative clinical trials. The clinical and microbiological results of the trials were good, and ofloxacin 0.3% ear drops, solution is considered an efficacious topical treatment of *AOM* and *CSOM* without severe adverse reactions. (The well-designed, evaluator-blinded, comparative study conducted by Goldblatt et al, 1998¹ demonstrated that the clinical efficacy of ofloxacin otic 0.3% solution ear drops was equivalent to that of Augmentin (amoxicillin and clavulanate) oral suspension 40 mg/per kg bodyweight per day, in *acute otitis media in pediatric subjects of 1 – 12 years of age with tympanostomy tubes*, and was at least as safe as Augmentin.

The multi-centre, open-label prospective trial study conducted by Agro et al, 1998² gives further support to the indication *Chronic Suppurative Otitis Media (CSOM) with purulent otorrhea and tympanic perforation*.

IV.5 Clinical safety

Following topical use of ofloxacin 3 mg/mL containing ear drops the systemic exposition is low. Ofloxacin UD 1.5 mg/0.5 mL ear drops may cause mild pain/discomfort in the ear, i.e., reaction at the application site. The most common reported adverse reactions in clinical trials in acute otitis media patients with tympanostomy tube and CSOM patients treated twice daily with ofloxacin 0.3% ototopic solution (n=656) were taste perversion (7%), earache (1%), pruritus (1%), paraesthesia (1%), rash (1%), and dizziness (1%)

However, a possibility of allergic reactions or changes in hearing remains.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ofloxacin Stulln Unit Dose.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	Potential for off-label use in children under one year Lack of efficacy
Missing information	Use in children younger than 6 months

¹ Goldblatt EL, Dohar H, Nozza RJ et al (1998): Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes, *Int J Pediatr Otorhinolaryngol* 46: 91-101 (abstract)

² Agro AS, Garner ET, Wright III JW et al (1998): Clinical trial of ototopical ofloxacin for treatment of chronic suppurative otitis media. *Clin Ther* 20: 744-759

The safety profile of ofloxacin can be considered to be well established and no product specific pharmacovigilance issues have been identified. Therefore the member states consider that routine pharmacovigilance measures are sufficient.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Oflocet ear drops, solution, which has the same indications as Ofloxacin Stulln Unit Dose. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The questionnaire consisted of 15 questions to assess the understanding of the contents of the PL, representing all the safety sections. In addition, there were 9 questions assessing the outside appearance of the PL and 5 questions regarding the reading behaviour. Overall, the interviews showed that the information of the PL was quickly found and well understood. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml, ear drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Oflocet ear drops, solution. Oflocet is a well-known medicinal product with an established favourable efficacy and safety profile.

As Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml, ear drops, solution is a product for auricular use (ear drops) intended to act without systemic absorption, with a comparable composition to the reference product, it is exempted for bioequivalence study.

The application was discussed in the Board meeting of 31 October 2013. It was noted that the Environmental Risk Assessment was incomplete. Furthermore the Board required that sections 4.1, 4.2, and 5.1 of the SmPC were to be amended, which the MAH followed. Overall, the Board expressed its positive opinion regarding the application for ofloxacin ear drops in the proposed indications.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ofloxacin Stulln Unit Dose 1.5 mg/0.5 ml, ear drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 October 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached