CILOXAN 3 mg/ml, ear drops, solution
B/1 bottle of 5 ml (CIP code: 3601303)

Applicant: ALCON FRANCE

Ciprofloxacin
ATC code: S02AA (antibiotic from the fluoroquinolone family)

List I

Date of Marketing Authorisation: 28 November 2002, amendment of 14 May 2008

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ciprofloxacin

1.2. Indication

"Antibiotic treatment for adults and children from 1 year:
- for acute otitis externa
- for purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation.
Consideration should be given to official guidance on the appropriate use of antibacterial agents."

1.3. Dosage

"Adults and Children 1 year and above

Acute otitis externa
In adults, the dose is 4 drops of solution in the affected ear 2 times per day.
In children, the dose is 3 drops of solution in the affected ear 2 times per day.
Treatment duration is 7 days.

Purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation.
In adults, the dose is 4 drops of solution in the affected ear 2 times per day.
In children, the dose is 3 drops of solution in the affected ear 2 times per day.
Treatment duration is 7 to 10 days.
For patients requiring use of an otowick, the dose can be doubled for the first administration only: 8 drops for adults and 6 drops for paediatric patients.

Dose adjustment in elderly patients is not necessary.

Method of administration
Topical – Instillation into the ear. Warm the bottle before use by holding it in the palm of the hand for several minutes to avoid the unpleasant sensation of introducing a cold solution into the ear.
Tilt the head to one side and put drops into the affected ear, pulling on the ear lobe several times. Keep the head tilted for approximately 5 minutes to allow the drops to penetrate into the external auditory canal. Repeat, if necessary, in the other ear.
When treatment is finished, discard the bottle. Do not keep it for re-use".
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

S: Sensory organs
S02: Otologicals
S02AA: Antiinfectives

2.2. Medicines in the same therapeutic category

- **Acute otitis externa**

CILOXAN is the only fluoroquinolone antibiotic with a Marketing Authorisation for this indication.

Note: OFLOCET 1.5 mg/0.5 ml, ear drops, solution in a single-dose container is also used in the treatment of otitis externa, without being explicitly indicated.

- **Purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation.**

<table>
<thead>
<tr>
<th>(INN) Products</th>
<th>Therapeutic indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFLOCET 1.5 mg/0.5 ml (ofloxacin),</td>
<td>“Topical treatment of purulent otorrhea:</td>
</tr>
<tr>
<td>ear drops, solution in single-dose</td>
<td>· of tympanostomy tubes,</td>
</tr>
<tr>
<td>container</td>
<td>· of the mastoid cavity,</td>
</tr>
<tr>
<td>Marketing Authorisation 1995</td>
<td>· of chronic suppurative otitis media with tympanic perforation.</td>
</tr>
<tr>
<td></td>
<td>Note: no trial has been carried out on otitis externa.</td>
</tr>
<tr>
<td></td>
<td>Consideration should be given to official guidance on the appropriate use of antibacterial agents.</td>
</tr>
</tbody>
</table>

2.3. Medicines with a similar therapeutic aim

Medicines with the same therapeutic aim are proprietary medicinal products for topical use, containing a single antibiotic or a combination of antibiotic(s) plus a corticosteroid. Preparations containing an aminoglycoside antibiotic (neomycin, framycetin) are contraindicated in cases of a perforated eardrum due to the risk of ototoxicity.
<table>
<thead>
<tr>
<th>(INN) products</th>
<th>Therapeutic indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute otitis externa</strong></td>
<td></td>
</tr>
<tr>
<td>POLYDEXA (neomycin 1 g or 650,000 IU/100 ml + polymyxin B 1,000,000 IU/100 ml + dexamethasone 0.1 g/100 ml)</td>
<td>Topical treatment of bacterial otitis externa with no tympanic perforation, specifically infected eczema of the external auditory canal. This medicinal product should never be used in cases of a perforated eardrum due to the risk of ototoxicity. Marketing Authorisation: 1977 BOUCHARA RECORDATI Laboratories</td>
</tr>
<tr>
<td>CORTICETINE (framycetin 630,000 IU/100 ml + dexamethasone 0.1 g/100 ml)</td>
<td>Topical treatment of bacterial otitis externa with no tympanic perforation, specifically infected eczema of the external auditory canal. This medicinal product should never be used in cases of a perforated eardrum due to the risk of ototoxicity. Marketing Authorisation: 1999 CHAUVIN Laboratory</td>
</tr>
<tr>
<td>FRAMYXONE (framycetin 0.7 g/100 ml + polymyxin B 700,000 IU/10 ml + dexamethasone 0.1 g/100 ml)</td>
<td>Topical treatment of bacterial otitis externa with no tympanic perforation, specifically infected eczema of the external auditory canal. This medicinal product should never be used in cases of a perforated eardrum due to the risk of ototoxicity. Marketing Authorisation: 1996 JOLLY-JATEL Laboratories</td>
</tr>
<tr>
<td>ANTIBIO-SYNALAR (neomycin 350,000 IU/100 ml + polymyxin B 1,000,000 IU/100 ml + fluocinolone 0.025 g/100 ml)</td>
<td>Topical treatment of bacterial otitis externa with no tympanic perforation, specifically infected eczema of the external auditory canal. This medicinal product should never be used in cases of a perforated eardrum due to the risk of ototoxicity. Marketing Authorisation: 1996 JOLLY-JATEL Laboratories</td>
</tr>
<tr>
<td>AURICULARUM (oxytetracycline, polymyxin B, dexamethasone, nystatin)</td>
<td>Topical treatment: · of bacterial and/or mycotic otitis externa; · of chronic otitis: · for pre-operative draining, · for post-operative use in petromastoid cavity with or without tympanoplasty. Contraindication: dry perforation of the eardrum Marketing Authorisation: 1987 GRIMBERG Laboratories</td>
</tr>
<tr>
<td>PANOTILE (neomycin 1 g/100 ml + polymyxin B 1,000,000 IU/100 ml + fludrocortisone 0.1 g/100 ml + lidocaine 3.2 g/100 ml)</td>
<td>Topical treatment of bacterial otitis externa with no tympanic perforation, specifically infected eczema of the external auditory canal. This medicinal product should never be used in cases of a perforated eardrum due to the risk of ototoxicity. Marketing Authorisation: 1996 ZAMBON Laboratory FRANCE</td>
</tr>
<tr>
<td><strong>Purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation.</strong></td>
<td></td>
</tr>
<tr>
<td>OTOFA (rifamycin 260 mg/10 ml)</td>
<td>Topical treatment of some types of purulent otorrhea: · of tympanostomy tubes, · of the mastoid cavity, · of chronic suppurative otitis media with tympanic perforation NB: rifamycin is inactive against <em>Pseudomonas aeruginosa</em> with many failed clinical and microbiological tests. This pathogen is responsible for at least 30% of infections for which this medicinal product is indicated. Marketing Authorisation: 1985 BOUCHARA RECORDATI Laboratory</td>
</tr>
</tbody>
</table>

Note: no trial has been carried out on otitis externa.
CILOXAN 3 mg/ml, ear drops, solution, obtained Marketing Authorisation on 28 November 2002, following a national procedure for the therapeutic indication in “topical treatment of acute bacterial otitis externa with no tympanic perforation”. This proprietary medicinal product was not marketed in France.

In a letter dated 14 February 2006, within the scope of the exemplification of the Marketing Authorisation decision following the updating of the Marketing Authorisations for ciprofloxacin-based products and the harmonisation of the drafting of the Marketing Authorisations containing antibiotics and administered by auricular route, AFSSAPS suggested to the ALCON laboratories to expand the indication for CILOXAN.

The Marketing Authorisation dated 14 May 2008 approved CILOXAN 3 mg/ml, ear drops, solution, for the indication “antibacterial treatment of adults and children from 1 year for acute otitis externa and for purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation”.

3.1. Efficacy

The main clinical trial carried out due to the request for Marketing Authorisation for CILOXAN 3 mg/ml in the indication of “Acute otitis externa” was a phase III study (C-98-18), which compared the efficacy of CILOXAN 3 mg/ml and CIPRODEX (combination of ciprofloxacin + dexamethasone, which does not have Marketing Authorisation in France) versus CORTISPORIN (combination of polymyxin sulfate B, neomycin base and hydrocortisone).

The extension of the indication to cover treatment of "for purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation", suggested by Afssaps, was obtained, based on a bibliographical review.

3.1.1. Acute otitis externa

In a controlled, randomised, blind phase III study (C-98-18), (carried out between 1998 and 2000), the efficacy of CILOXAN 3 mg/ml and CIPRODEX (a combination of ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml) was compared with that of CORTISPORIN (a combination of polymyxin B 10,000 IU/ml, neomycin 3.5 mg/ml and hydrocortisone 10 mg/ml), over a treatment duration of seven days.

CIPRODEX and CORTISPORIN do not have Marketing Authorisations in France.

At inclusion, the patients had moderate to severe acute otitis externa, were at least 1 year old and had the following symptoms: slight oedema, moderate inflammation and painful sensitivity.

Patients with a perforated or modified eardrum could not be included in this trial.

A total of 909 adult and paediatric patients (mean age 21 years) were included in the study (CILOXAN, n=305; CIPRODEX, n = 305 and CORTISPORIN, n=299). The proportion of positive cultures was similar in the three groups (68 to 70%) with a predominance of \textit{Pseudomonas aeruginosa} and \textit{Staphylococcus aureus}, the two most common species found in this disease.

1 CORTISPORIN is not marketed in France; there are compositions close to this category of proprietary medicinal products marketed in France, comprising the combination of two antibiotics (aminoglycoside + polypeptide) and a corticosteroid, such as POLYDEXA and PANOTILE.
The aim of the study was to demonstrate the non-inferiority (delta threshold = 10%) of CILOXAN compared with CORTISPORIN, in terms of clinical response at the check-up visit at D+18 days.

From per protocol analysis, the non-inferiority of CILOXAN versus CORTISPORIN was demonstrated, in terms of clinical healing: 95.5 % versus 91.2% (95% CI of the difference: [-0.9; 8.79]). From the ITT analysis, the rates of healing were 81.9% versus 80.9% (95% CI of the difference: [-5.2; 7.2], p=0.74).

In patients with a positive culture at inclusion, the rates of healing were 96.3% versus 91.0% (95% CI of the difference: [0.55; 9.97], p=0.03). This response was 98.2% versus 91.6% (95% CI of the difference: [0.43; 12.71], p=0.05) in the paediatric population (0 - 12 years).

The rates of healing were 95.8% versus 88.9% (p=0.03) for patients with a positive P. aeruginosa culture and 95.5% versus 83.3% (p<0.01) for those with a positive Gram positive bacteria culture. The rates of bacterial eradication were similar between the two treatment groups (95.3% versus 92.0%).

The rates of clinical and bacteriological response were also similar between CILOXAN and CIPRODEX.

Four previous publications more specifically concerning the treatment of acute otitis externa were included in the file. It should be noted that the concentration of ciprofloxacin evaluated (2 mg/ml) in these studies does not correspond to those of CILOXAN (3 mg/ml).

<table>
<thead>
<tr>
<th>Published trial</th>
<th>Type of trial</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganz, 1989</td>
<td>Open-label</td>
<td>34</td>
<td>Ciprofloxacin 2 mg/ml</td>
<td>Clinical efficacy 86%</td>
</tr>
<tr>
<td>Arnes et al., 1993</td>
<td>Controlled</td>
<td>30</td>
<td>Ciprofloxacin 2 mg/ml (16 patients)</td>
<td>Clinical efficacy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxytetracyxin 5 mg/ml / polymyxin B</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10,000 U / hydrocortisone 15 mg/ml</td>
<td>35.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(14 patients)</td>
<td></td>
</tr>
<tr>
<td>De Schepper et al., 1994</td>
<td>Open-label</td>
<td>17</td>
<td>Ciprofloxacin 2 mg/ml</td>
<td>Clinical and microbiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>efficacy: 17/17</td>
</tr>
<tr>
<td>Pistorius et al., 1999</td>
<td>Controlled,</td>
<td>842</td>
<td>Ciprofloxacin 2 mg/ml</td>
<td>Clinical efficacy:</td>
</tr>
<tr>
<td></td>
<td>randomised</td>
<td></td>
<td>Ciprofloxacin 2 mg/ml + Hydrocortisone</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg/ml Cortisporin</td>
<td></td>
</tr>
</tbody>
</table>

3.1.2. Purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation

No specific clinical trial has been carried out for this indication with CILOXAN 3 mg/ml, ear drops, solution. 
A literature review described the use of fluoroquinolone antibiotics, such as ciprofloxacin solution for auricular use, with different dosage regimens and treatment durations (5 to 21 days) in adult and paediatric patients (see Appendix).\(^6\)

The efficacy results from these studies suggest that the topical use of ciprofloxacin 3 mg/ml would be at least as effective as using ear drops containing aminoglycosides. The topical use of ciprofloxacin was more effective than the systemic use of ciprofloxacin.

It should be noted that the clinical studies included in this review are old (carried out between 1986 and 1999) and of poor methodological quality: different dosage regimens, low number of patients, the absence of placebo group or the absence of randomisation, depending on the study.

3.2. Adverse effects

From the clinical study (C-98-18) carried out on adult and paediatric patients with moderate to severe acute otitis externa with no tympanic perforation (N=909 patients, of which 305 were treated with CILOXAN), no serious adverse effects were reported and no patient stopped treatment due to the occurrence of an adverse effect. The most common adverse effects were ear canal pruritus and a burning sensation when putting in the drops.

The clinical experience reported on the use of ciprofloxacin ear drop solution highlighted no major tolerance concerns in using this antibiotic.
According to the SPC, the reported adverse effects when using this medicinal product with a frequency between 0.3% and 1.3% were: itching of the ear canal, tinnitus, headaches and dermatitis.
Also highlighted was the risk of contact eczema and irritation due to the presence of benzalkonium chloride.

A warning was included (see Section 4.4) stating that the administration of topical antibiotics may lead to sensitivity to these active substances, with the possibility of systemic reactions occurring. It is recommended to discontinue the treatment at the first appearance of a skin rash or any other sign of hypersensitivity.

---

\(^6\) Appendix 1: literature review of the Marketing Authorisation file for the indication "purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation"
3.3. Conclusion

For otitis externa, ciprofloxacin 3 mg/ml, ear drop solution, is at least as effective as a set combination of aminoglycoside/polypeptide/corticosteroid in ear drops, with a rate of clinical healing greater than 90% after seven days of treatment. For purulent otorrhea, data from the literature also shows a clinical efficacy of ciprofloxacin 3 mg/ml, ear drops solution at least equal to that of ear drops that contain aminoglycosides.

There have been no clinical studies versus ofloxacin (OFLOCET)⁷ which represent a quinolone-based therapeutic alternative, especially for perforated eardrums, which is a contraindication in the use of aminoglycosides. However, *in vitro*⁸ activity of ciprofloxacin towards the main pathogens encountered in these diseases (particularly *Pseudomonas aeruginosa* and *Staphylococcus aureus*) and the response rates described in the literature⁹ on the use of these two quinolones do not appear to be in favour of a lower clinical efficacy for ciprofloxacin.

The clinical experience reported on the use of the ciprofloxacin ear drop solution, did not highlight any major tolerance concerns in using this antibiotic.

---

⁷ OFLOCET (Marketing Authorisation of 21/11/1995), ear drops solution, has a Marketing Authorisation for purulent otorrhea. It is also used in the treatment of otitis externa, without being explicitly indicated.

⁸ *Ciprofloxacin is the fluoroquinolone with the best activity against Pseudomonas aeruginosa.*

⁹ See Appendix 2. AFSSAPS guidelines "topical antibiotic therapy in ENT" of July 2004: Efficacy data of different antibiotics.
4.1. Actual benefit

Acute otitis externa and purulent bacterial otitis are not normally serious.

CILOXAN 3 mg/ml, ear drops, solution, is intended as curative treatment.

The efficacy/adverse effects ratio for CILOXAN 3 mg/ml is high.

There are treatment alternatives. However, CILOXAN is the only antibiotic with a Marketing Authorisation (MA) for the treatment of acute otitis externa in cases of a perforated eardrum. Indeed, the other fluoroquinolone ear drop solution in a single-dose container, OFLOCET (ofloxacin), with a Marketing Authorisation for purulent otitis externa is also used outside of the Marketing Authorisation for the treatment of acute otitis externa.

Public health benefit

In terms of public health benefit, the burden represented by bacterial otitis externa is low, despite its frequency, as it is not normally serious. Nevertheless, it is the cause of numerous consultation appointments and absences from school.

The management of bacterial otitis is not an established public health priority.

In the absence of comparative data versus ofloxacin on the one hand, and data on otitis externa with tympanic perforation on the other, and based on a single non-inferiority trial versus a set combination of two antibiotics (aminoglycoside/polypeptide) and a corticosteroid, an additional impact is not expected for CILOXAN on the morbidity of otitis externa. The impact of CILOXAN on the morbidity of purulent otitis externa cannot be estimated due to the poor methodological quality of the clinical studies presented.

Consequently, CILOXAN is not expected to be a public health benefit in its indications.

The actual benefit of CILOXAN 3 mg/ml, ear drops solution is substantial in the Marketing Authorisation indications.

4.2. Improvement in actual benefit (IAB)

- **In the indication "acute otitis externa"**

Given,

- the demonstrated clinical efficacy of ciprofloxacin (CILOXAN) in acute otitis externa without tympanic perforation, compared with an ear drops solution containing a set combination of two antibiotics (aminoglycoside/polypeptide) and a corticosteroid,
- the possible use in cases of a perforated eardrum (although the ototoxicity risk contraindicates the intra-auricular use of aminoglycosides),
- the microbiological activity towards the main pathogens encountered in this disease (particularly *Pseudomonas aeruginosa* and *Staphylococcus aureus*),
- the good tolerance profile
- the absence of a therapeutic alternative with a Marketing Authorisation in this indication in cases of tympanic perforation,

the Transparency Committee considered that CILOXAN provides a minor improvement in actual benefit (IAB IV) in the management of acute otitis externa.
In the indication "purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation"

The Committee considers that CILOXAN does not provide an improvement in actual benefit (IAB V) compared with OFLOCET, ear drops solution, which has a Marketing Authorisation (MA of 21/11/1995) in this indication.

The Committee recognises that CILOXAN represents a beneficial therapeutic alternative given its good efficacy and tolerance profile and its in vitro microbiological activity towards the main pathogens encountered in this disease (in particular Pseudomonas aeruginosa and Staphylococcus aureus).

4.3. Therapeutic use

Topical antibiotics for auricular use should never be used in cases of acute otitis media, either congestive or purulent, or for otitis media with effusion as their benefit has not been demonstrated in these situations.

The role of topical antibiotics for auricular use is included in the AFSSAPS guidelines “topical antibiotic therapy in ENT” of July 2004.

Topical antibiotics for auricular use are beneficial in well defined situations, otitis externa, otorrhea from chronic otitis with tympanic perforation and otorrhea from tympanostomy tubes, for which the symptom duration is reduced. However, auricular ototoxic presentations can only be used once the absence of tympanic perforation has been verified.

Otitis externa

Otitis externa is an infectious dermatological condition of the skin of the external auditory canal. The basic treatment for otitis externa is with topical antibiotics. Systemic use of antibiotics may also be co-administered in certain medical situations linked to the predisposition (primarily diabetes and malignant otitis externa*) or locoregional spreading of the otitis.

It is desirable to carry out a thorough otoscopic examination to eliminate the possibility of a perforated eardrum (rare in otitis externa) and, if possible, carefully clean the external auditory canal. In cases of a narrowed ear canal, it is recommended to place an expanding plug into the canal, to allow good penetration of the drops and to maintain a high topical concentration of antibiotics.

Due to the rarity of perforated eardrums in otitis externa, the use of preparations containing aminoglycosides is allowed, except for patients with a known perforation or a previous medical history of possible perforation. In these instances, fluoroquinolones are effective and safe to use.

The usual treatment duration is seven days with a frequency of two to four applications per day. Topical treatment also includes an anaesthetic or corticosteroids, as this disease can be painful. Generally, systemic analgesic treatment is also necessary.
Specific case of malignant otitis externa

This is a rare and particularly serious clinical presentation of otitis externa due to P. aeruginosa that is mainly observed in diabetics, but also in the extremely elderly or immunocompromised. It requires urgent treatment with IV antipyocyanic antibiotic therapy and a specialised surgical procedure. This infection can rapidly lead to a life-threatening prognosis and may also result in serious consequences (in particular facial paralysis). Treatment will be extended as it is nearly always accompanied by locoregional osteitis.

Place of CILOXAN in the treatment of otitis externa

CILOXAN 3 mg/ml, ear drops solution, the main active ingredient of which ciprofloxacin is part of the fluoroquinolone family, is a first-line medicinal product in the treatment of acute bacterial otitis externa. It is the first fluoroquinolone-based proprietary medicinal product for auricular use to have a Marketing Authorisation for acute otitis externa.

- Chronic suppurative otitis media with tympanic perforation
  Topical antibiotic therapy, associated with the cleaning of the external auditory canal, is the basic treatment for this disease. Fluoroquinolones are the first-line treatment as they have an appropriate anti-microbial spectrum of activity for the pathogens most commonly encountered in this disease and are not ototoxic. Other molecules may also be used, with the exception of aminoglycosides (neomycin, framycetin), which are contraindicated due to the risk of ototoxicity.
  There is no need to take a sample for first-line treatment.
  If treatment fails, a return visit to the ENT department is recommended for a fine-needle aspiration for bacteriological testing, especially in children. In such cases, systemic treatment may be started.

Role of CILOXAN in the treatment of otorrhea from chronic suppurative otitis media

CILOXAN 3 mg/ml, ear drops solution, is an alternative to OFLOCET (ofloxacin), ear drops solution (Marketing Authorisation of 21/11/1995) as a first-line treatment of otorrhea from chronic suppurative otitis media.

- Otorrhea from tympanostomy tubes
  When it is isolated, with no associated systemic signs, topical antibiotic therapy with fluoroquinolones (only ofloxacin has a Marketing Authorisation in this indication) is the first-line treatment, after cleaning of the external auditory canal.
  Ototoxic products may not be used in this situation. In cases of persistent symptoms or in the presence of systemic signs, thin-needle aspiration for bacteriological testing is recommended, before changing ear drops or implementing systemic antibiotic therapy.
  CILOXAN 3 mg/ml, ear drops solution does not have a Marketing Authorisation in this indication.

---

4.4. Target population

According to data from the Observatoire de la Médecine Générale (in 2009) otitis externa represented 1% of general practitioner consultation appointments. In 2009, each generalist physician saw an average of 13.2 patients for every 15.1 cases of indicated otitis externa.\textsuperscript{11}

If these figures are compared to the number of general practitioners (101,667 in 2009),\textsuperscript{12} the number of general practitioner consultations for otitis externa may be estimated at approximately 1,500,000. This figure does not take into account the consultations with medical specialist (ENT and paediatricians). Furthermore, these data do not allow to estimate the frequency of antibiotics prescriptions from consultations for otitis externa.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use and various public services in the indications and at the dosage indicated in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

\textsuperscript{11} Observatoire de la Médecine Générale: Informations épidémiologiques sur les pathologies et leur prise en charge en ville. http://omg.sfmg.org/

\textsuperscript{12} INSEE : Professions de santé. Available at: http://insee.fr/fr/themes/tableau.asp?ref_id=NATTEF06103
Appendix 1:

**Literature review for the indication "purulent otorrhea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation"**

3.1.3. **Ciprofloxacin in Chronic Suppurative Otitis Media (CSOM)**

Chronic suppurative otitis media (chronic otitis media) refers to a chronic discharge from the middle ear through a perforation of the tympanic membrane. Suppurative refers to active clinical infection; a perforation without discharge can be an inactive stage of the infection (Klein et al. 1999). The traditional medical treatment has combined aural toilet with systemic or topical treatment with antibiotic(s) alone or in combination with a steroid (Pincus et al., 1997).

- Van De Heyning et al. (1986, 1988) administered ciprofloxacin 750 mg BID orally for two weeks to a total of 53 chronic suppurative otitis media patients. Ciprofloxacin treatment eradicated 68.3% of pathogens and resulted in clinical improvement or resolution in 77.5% of patients.

- Falser et al. (1988) gave ciprofloxacin 500 mg BID orally or penicillin V 2000 mg TID orally for 10 days to 35 otitis media patients with an average age of 39 years (range 19 to 76). Ciprofloxacin treatment was more effective than penicillin in clinical efficacy (60% compared to 48%) and bacterial eradication (57% compared to 43%). Both drugs were well tolerated, with no reported side effects.
• Piccirillo et al. (1989) reported that 18 of 19 evaluable patients with chronic ear disease, treated with 500 mg oral ciprofloxacin BiD for two weeks, showed clinical improvement or cure with no side effects.

• Esposito et al. (1990) conducted a 60-patient, controlled clinical trial of ciprofloxacin given either (i) 250 mg orally BID; (ii) 3 drops of 2.5 mg/ml solution given topically BID; or (iii) oral and topical treatment for 5-10 days to CSOM patients (average age of 38 years). Favourable clinical response (100% and 95%) and bacterial eradication (95% and 85%) were noted in groups (ii) and (iii) with a lower response to oral therapy alone (65% and 40% cures). No auditory or vestibular effects were noted.

• The same group (Esposito et al., 1992) then published a 60-patient, controlled, 5-10 day clinical study of topical ciprofloxacin 2.5 mg/ml solution (4 drops BID) compared to intramuscular gentamicin (80 mg BID) treatment for CSOM (with perforated tympanic membrane). The average patient age was 39 years (range 18 to 65). Favourable clinical results were obtained in 26/30 (87%) of patients treated with ciprofloxacin, compared to 20/30 (66%) of patients treated with gentamicin. No side effects and no worsening of audiometric function were reported.

• Rodriguez et al. (1993) reported on a 63-patient pilot study comparing the effectiveness of oral ciprofloxacin (500 mg every 12h for 7 days) with topical ciprofloxacin (2 mg/ml solution, 3 drops TID for 7 days) and a combination of oral and topical dosing for therapy of ear infections, including CSOM. The average patient age was 38 years. Treatment with topical ciprofloxacin was significantly more effective than treatment with oral ciprofloxacin in terms of clinical improvement or cure (95.2% v. 68.2%) or bacterial eradication (95.2% v. 54.5%). Pseudomonas was the main pathogen isolated. Results with the combined therapy did not show any significant difference. Oral ciprofloxacin was more effective than oral amoxicillin in CSOM patients.

• Logent et al. (1994) conducted a 76-patient, controlled study comparing ciprofloxacin (500 mg oral BID) to amoxicillin/clavulanic acid (500 mg oral TID) for 9 days in CSOM patients (average patient age of 41 to 46 years). Clinical cures were reported in 57.5% of the ciprofloxacin group compared to 37.1% in the amoxicillin group. Similarly, bacterial eradication was higher for ciprofloxacin (69.7%) compared to amoxicillin (27.3%). Both treatments were well tolerated.

• Lorente et al. (1995) reported on a large, 308-patient, controlled study to evaluate efficacy and tolerance of topical ciprofloxacin (3 mg/ml solution, 3 drops BID for 8 days) compared to gentamicin (3 mg/ml solution, 3 drops BID for 8 days). The average patient age was 42 years (range 18 to 65). For safety purposes, one group of 5 patients was treated with 0.75% ciprofloxacin solution for up to 30 days. Of 308 patients enrolled, 159 were treated with ciprofloxacin and 149 with gentamicin. The percentage of clinical success (absence of otorrhea) was 95% for ciprofloxacin and 94% for gentamicin. Similarly, the percentage of bacterial eradication was 96% for ciprofloxacin and 93% for gentamicin. Both drugs were well tolerated without changes in audiometric values.

• Tutkun et al. (1995) conducted a smaller, 44-patient, controlled study to compare the therapeutic efficacy of topical ciprofloxacin (2 mg/ml solution) with topical gentamicin (5 mg/ml solution) when administered as 5 drops TID for 10 days. The average age was 28 years (range 9 to 65). Of 44 patients enrolled, 24 were treated with ciprofloxacin and 20 with gentamicin. The clinical cure rate (dry ear) was significantly greater for ciprofloxacin (88%) compared to gentamicin (30%). There were no side effects or hearing loss produced by either agent. The study concluded that topical ciprofloxacin treatment was more effective than topical gentamicin therapy in the treatment of CSOM.

• Rodriguez et al. (1995) conducted a 62-patient, controlled study to evaluate the efficacy and safety of ciprofloxacin given orally (500 mg every 12h for 10 days) compared to topical dosing (2.5 mg/ml solution, 3 drops BID for 10 days) in the treatment of CSOM. The
average patient was 45 years old. Clinical cure and microbiological eradication were significantly greater for topical dosing (85% and 95%) compared to oral administration (50% and 60% respectively). No ototoxicity associated with ciprofloxacin was reported.

- Sabater et al. (1996) provided a 101-patient, controlled study to compare topical ciprofloxacin (5 mg/ml solution) to topical gentamicin (3 mg/ml solution) in the treatment of CSOM and diffuse external otitis. Of 101 patients enrolled, 47 patients were diagnosed with CSOM and 54 patients with external otitis. Clinical success rate (dry ear) was 95% for ciprofloxacin and 98% for gentamicin in the CSOM group. Corresponding results in the diffuse external otitis group were 87% for ciprofloxacin and 79% for gentamicin. Both drugs were well tolerated, and no significant changes were noted in audiometric function. The study concluded that ciprofloxacin is at least as effective as gentamicin, and no observable ototoxicity was reported.

- Fradis et al. (1997) evaluated the efficacy of ciprofloxacin (2 mg/ml solution) compared to tobramycin (3 mg/ml solution) and placebo ear drops (five drops TID for 3 weeks) in 51 patients (60 ears) with chronic suppurative otitis media (CSOM). The clinical response was 78.9%, 72.2% and 41.2% in the ciprofloxacin, tobramycin and placebo groups, respectively. The bacteriologic response rate was 66.7% for ciprofloxacin and tobramycin and 20% for the placebo group. The study concluded that treatment of CSOM patients with ciprofloxacin was equivalent to tobramycin therapy.

- Kasemsulan et al. (1997) reported on a 35-patient, double-blind study to evaluate the effectiveness of topical ciprofloxacin (2.5 mg/ml solution) versus normal saline solution in the treatment of patients with an acute episode of CSOM. In the group of 19 patients receiving ciprofloxacin (5 drops TID for 7 days), favourable clinical responses (cure plus improvement) were observed in 89.5% compared to 43.8% in the saline treated control group. The bacterial eradication rate was 84.2% in the ciprofloxacin group, and 12.5% in the saline-treated group. Audiology data showed no hearing loss in ciprofloxacin-treated patients. The authors concluded that topical ciprofloxacin was safe and effective in the treatment of the acute phase of CSOM.

- Podoshin et al. (1998) evaluated the efficacy of topical ciprofloxacin (2 mg/ml solution) ear drops compared to tobramycin (3 mg/ml solution) and saline solution in the treatment of CSOM. A total of sixty ears were randomised to treatment. Clinical responses were 78.9% and 72.2%, respectively in the ciprofloxacin and tobramycin groups compared to 41.2% in the saline placebo group. The study concluded that treatment of CSOM patients with ciprofloxacin was similar in effectiveness to tobramycin treatment.

- Kiris et al. (1998) evaluated 80 patients with otitis due to CSOM treated with ciprofloxacin ear drops, in two settings. One group received daily ciprofloxacin therapy plus aspiration in the clinic. The other group self-administered at home. Overall otitis resolved in 80% of all ears within 12 days of treatment initiation. There were no significant differences in success rates between the two groups. Adverse effects were negligible. They concluded that empirical topical ciprofloxacin therapy was an effective, safe and relatively inexpensive treatment in patients with otitis and chronic otitis media.

- Indudharan et al (1999) undertook a bacteriologic examination of isolates from patients treated for chronic suppurative otitis media in Malaysia. They reported that S. aureus was almost completely resistant to ampicillin and polymyxin B and P. aeruginosa to ampicillin and chloramphenicol. Among the available antibiotic preparations for use in the ear they concluded that ciprofloxacin and gentamicin were the best choices.

- De Miguel Martinez et al., (1999) conducted a randomised study of 125 patients with CSOM. Three treatment groups were assigned; oral ciprofloxacin, 5 mg/ml or 2 mg/ml topical ciprofloxacin or topical polymyxin and neomycin. Topical ciprofloxacin 2 mg/ml was the most effective regimen of those tested for the treatment of chronic otitis media.
Appendix 2: (Extracts from recommendations "topical antibiotic therapy in ENT" of July 2004).

- **Efficacy of auricular antibiotics in the treatment of otitis externa**
  
  **Fluoroquinolones**
  
  The efficacy of ofloxacin in the treatment of otitis externa is estimated at 82% for adults and 97% for children.\(^\text{13}\)
  
  It does not have a Marketing Authorisation in this indication. Ciprofloxacin has an estimated clinical efficacy of 93%, regardless of age.\(^\text{14}\)
  
  **Neomycin-Polymyxin B-Hydrocortisone**
  
  The estimated clinical efficacy of this combination is 87% regardless of age\(^1\), 84% for adults and 95% for children.
  
  **Colimycin, Framycetin, Oxytetracycline-Polymyxin B**
  
  These antibiotics, alone or in combinations, have Marketing Authorisation in this indication. However, there is no published clinical study, except for the combination of oxytetracyclin-polymyxin B-hydrocortisone that demonstrates a clinical efficacy of 80% regardless of age.\(^\text{15}\)

- **Efficacy of auricular antibiotics in the treatment of "chronic suppurative otitis media with tympanic perforation"**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Legent(^\text{16}) N=76</th>
<th>Miro(^\text{17}) N=232</th>
<th>Tong(^\text{18}) N=52</th>
<th>Pessey(^\text{19}) N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>57%</td>
<td>91%</td>
<td>89%</td>
<td>91.6%</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>70%</td>
<td>89%</td>
<td>91%</td>
<td>95.8%</td>
</tr>
<tr>
<td>Neomycin polymyxin hydrocortisone</td>
<td>87%</td>
<td>79%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Neomycin polymyxin hydrocortisone</td>
<td>87%</td>
<td>79%</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>


\(^{17}\) Miro N and the Spanish ENT study group. Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single dose containers or combination of polymyxin B, neomycin and hydrocortisone suspension. Otolaryngol Head Neck Surg 2000; 123: 617-23
