HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

# TRANSPARENCY COMMITTEE

## Opinion

## 29 May 2013

## CILOXADEX 3 mg/1 mg per ml, ear drops, suspension

**Box of 1 dropper container of 5 ml (CIP: 34009 224 397 1 6)**

Applicant: ALCON

| | |
|---|---|
| INN | - ciprofloxacin 3 mg<br>- dexamethasone 1 mg |
| ATC Code (year): | S02CA06 (antiinfectives and dexamethasone in combination) |
| Reason for the request | **Inclusion** |
| List(s) concerned | **National Health Insurance** (French Social Security Code L.162-17)<br>**Hospital use** (French Public Health Code L.5123-2) |
| Indication(s) concerned | **"Treatment of the following infections in adults and children**<br>• **Tympanostomy tube otorrhoea.**<br>• **Acute otitis externa."** |

| | |
|---|---|
| **Actual Benefit** | **moderate** |
| **Improvement in Actual Benefit** | CILOXADEX does not offer any improvement in actual benefit (IAB V, nonexistent) compared with topical antibiotics for auricular use belonging to the fluoroquinolone class of antibiotics (antibiotic alone without corticosteroid: ciprofloxacin or ofloxacin) currently on the market in the management of acute otitis externa and tympanostomy tube otorrhoea. |
| **Therapeutic use** | - In acute otitis externa, topical antibiotic therapy relies for a first-line treatment on the use of the fluoroquinolone class of antibiotics (ciprofloxacin, ofloxacin) or of a preparation containing aminosides, except in cases of perforated eardrum on account of the risk of ototoxicity. Of all the fluoroquinolones, only ciprofloxacin (CILOXAN or CETRAXAL) has Marketing Authorisation specifically in this indication. CILOXADEX (fixed combination of ciprofloxacin + dexamethasone) is a new treatment option to using ciprofloxacin by itself. However, the clinical benefit of dexamethasone has not been demonstrated in relation to the use of ciprofloxacin alone.<br>- In patients with tympanostomy tube otorrhoea, topical antibiotic therapy relies in the first instance on the use of fluoroquinolone antibiotics (at the present time only ofloxacin has Marketing Authorisation specifically in this indication). Rifamycin (OTOFA) also has Marketing Authorisation in this indication, but it is inactive against *Pseudomonas aeruginosa*, with frequent clinical and microbiological failures. CILOXADEX (fixed combination of ciprofloxacin + dexamethasone) is a new treatment alternative to using ciprofloxacin alone or ofloxacin. Adding dexamethasone to an antibiotic could make for faster drainage of the otorrhoea than the topical antibiotic on its own; however, the benefit of such an effect has yet to be established, and a corticosteroid-related risk (decreased immune response, masking of the clinical signs of infection) cannot be ruled out. |
| **Recommendation** | |

# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

| | |
|---|---|
| Marketing Authorisation (procedure) | Initial date: 14/12/2012 (centralised procedure) |
| Prescribing and dispensing conditions/ special status | List I |

| | |
|---|---|
| ATC Classification | 2012<br>S : Sensory organs<br>S02 : Otologicals<br>S02CA : Corticosteroids and antiinfectives in combination<br>S02CA06 : Dexamethasone and antiinfectives |

# 02 BACKGROUND

*This Opinion concerns an application for inclusion on the list of medicinal products refundable by National Health Insurance and approved for hospital use of a fixed combination containing a fluoroquinolone antibiotic (ciprofloxacin) and a corticosteroid (dexamethasone) for the treatment of "acute otitis externa" and "tympanostomy tube otorrhoea".*
At the present time there are two medicinal products containing only ciprofloxacin (CILOXAN and CETRAXAL). On the other hand, there are no otic medicinal products containing dexamethasone alone available on the market.

At the present time, CILOXADEX are the first ear drops containing fluoroquinolone (ciprofloxacin) and corticosteroid (dexamethasone) to have Marketing Authorisation in these indications.

# 03 THERAPEUTIC INDICATION(S)

"CILOXADEX is indicated in the treatment of the following infections in adults and children (see Section 4.2 of the SPC). See Section 5.1 of the SPC for the generally sensitive species.
- Tympanostomy tube otorrhoea.
- Acute otitis externa.
The official guidelines on the appropriate use of antibacterial agents should be taken into consideration."

# 04 DOSAGE

**Dosage**

Adults and elderly subjects
Instil four drops into the affected ear(s) twice a day for 7 days according to the different instillation instructions for patients with tympanostomy tube otorrhoea and patients with acute otitis externa.
Generally, no differences in safety of use and effectiveness have been observed between elderly and other adult patients.

Paediatric population
This medicine has been shown to be safe and effective in children aged 6 months of age and older for the treatment of tympanostomy tube otorrhoea and children 1 year of age and older for the treatment of acute otitis externa (see Section 4.4 of the SPC for use in children younger than 6 months with tympanostomy tube otorrhoea and in children younger than 1 year acute otitis externa). CILOXADEX can be used at the same dose as in adults (see Section 5.2 of the SPC).

Patients with hepatic or renal impairment
Hepatic or renal impairment (mild to moderate) does not alter the pharmacokinetics of ciprofloxacin or dexamethasone when administered systemically.
Following topical otic administration of CILOXADEX ear drops, small increases in the ciprofloxacin and dexamethasone plasma concentrations may be observed in patients with severe renal or hepatic impairment. However, since systemic exposure to ciprofloxacin or dexamethasone is low in cases of topical otic administration, any increase in systemic concentrations due to renal or hepatic dysfunction would still be well below the plasma concentrations that are well tolerated in children or adults receiving the recommended doses by the oral or intravenous route.
There is no necessity for dose adjustment of this medication in patients with renal or hepatic dysfunction.

**Method of administration**

Instillation into the ear (see SPC).

# 05 THERAPEUTIC NEED

**Topical antibiotics for auricular use should not be used in cases of acute otitis media, either congestive or purulent, nor in seromucous otitis, because their value is not proven in these situations.**

The place of topical antibiotics for auricular use is described in the latest French guidelines on "local antibiotic therapy in ENT" of July 2004.[1]
Topical antibiotics for instillation into the ear are beneficial (reducing how long the symptoms last) in certain well-defined situations: otitis externa, chronic suppurative otitis media with tympanic perforation, and tympanostomy tube otorrhoea. However, ototoxic topical antibiotics (aminosides) cannot be used until after tympanic perforation has been ruled out.

- Otitis externa

Otitis externa is dermo-epidermitis of the external auditory canal of infectious origin, for which the basic treatment is a topical antibiotic. Systemic antibiotic therapy 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 rule out the possibility of a perforated eardrum (rare in otitis externa) and, if possible, carefully clean the external auditory canal. In cases where the ear canal has narrowed, 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 in use.

[1] Available on the SPILF (French Infectious Diseases Society) website:
http://www.infectiologie.com/site/medias/_documents/consensus/2004-atb-locale-ORL-recos-afssaps.pdf

The usual treatment duration is 7 days with a frequency of 2 to 4 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[2]

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 very elderly or immunocompromised individuals. It requires urgent treatment with intravenous antipyocyanic antibiotic therapy and a specialised surgical procedure. This infection can quickly 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.

- Chronic suppurative otitis media with tympanic perforation

Topical antibiotic therapy, together 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 (rifamycin) 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.

- Tympanostomy tube otorrhoea

Systemic antibiotic therapy is indicated in cases of tympanostomy tube otorrhoea when there are systemic signs suggesting the presence of acute otitis media.

When it is isolated, with no associated systemic signs, topical antibiotic therapy is the first-line treatment, after cleaning of the external auditory canal.
Topical antibiotic therapy with fluoroquinolones is the first-line treatment (currently only ofloxacin has Marketing Authorisation in this indication). 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.

## Coverage of therapeutic need

Therapeutic need is currently covered by 9 topical antibiotics for instillation into the ear:

1. Four combine "polymixin B, neomycin, and *corticosteroid*" [ANTIBIO SYNALAR, FRAMYXONE, PANATILE, POLYDEXA]. The wording of the indications is the same: "*Topical treatment of bacterial otitis externa with no tympanic perforation, specifically infected eczema of the external auditory canal.* ***This medicine should not be used in cases of perforated eardrum owing to the risk of ototoxicity".*** They all have a "moderate" actual benefit, because they are a combination of antibiotic and corticosteroid.
2. One medicinal product combines Oxytetracycline, Polymixine B, *Dexamethasone* and Nystatin [AURICULARUM]. The actual benefit is substantial. The justification for the substantial actual benefit is the presence of Nystatin (antifungal).
3. One medicinal product based on rifamycin alone [OTOFA]. Because of this, its indications include some special reservations:
   *Topical treatment of some types of purulent otorrhoea:*
   - *tympanostomy tube,*
   - *of the mastoid cavity,*
   - *of chronic suppurative otitis media with tympanic perforation.*

[2]. CMIT (French College of Infectious and Tropical Diseases) Otites. In E. Pilly: Vivactis Plus Ed; 2012: pp 163 - 167

*NB: Rifamycin is inactive against Pseudomonas aeruginosa, with frequent clinical and microbiological failures. This pathogen is responsible for at least 30% of infections for which this medicinal product is indicated. Note: No studies have been performed in otitis externa.*
Its actual benefit is substantial (because it is an antibiotic alone).

4. Finally three fluoroquinolones (antibiotic alone), which allow coverage of all the indications as well as all age groups from 1 year, with different wordings for the indications:
   - ofloxacin [OFLOCET]
   - ciprofloxacin [CILOXAN and CETRAXAL]

   These topical quinolones are necessary for the treatment of otitis externa and infections with tympanic perforation. All of them have a “substantial” actual benefit.

**The composition of CILOXADEX combines a fluoroquinolone antibiotic (ciprofloxacin) and a corticosteroid (dexamethasone). It thus constitutes a new option that needs to be assessed in comparison with topical fluoroquinolone antibiotics (antibiotic alone with no corticosteroid: ciprofloxacin or ofloxacin) currently on the market.**

# 06 CLINICALLY RELEVANT COMPARATORS

## 06.1 Medicinal products

CILOXADEX is the only antibiotic for auricular use combining a fluoroquinolone (ciprofloxacin) and a corticosteroid (dexamethasone).

➢ **Proprietary medicinal products for topical use containing an antibiotic alone**

| Proprietary medicinal product (INN) | Therapeutic indications | Committee opinion |
|---|---|---|
| **Fluoroquinolone antibiotics: Marketing Authorisation in <u>otitis externa</u> (with or without tympanic perforation) and <u>otorrhoea</u>** | | |
| CETRAXAL 2 mg/ml (ciprofloxacin) ear drops<br>Marketing Authorisation: 01/08/2011<br>Applicant: LEURQUIN MEDIOLANUM S.A. | "Treatment of acute otitis externa with no tympanic perforation due to ciprofloxacin-sensitive bacteria. The official guidelines on the appropriate use of microbiocides must be taken into consideration." | <u>15 February 2012</u><br>- AB: substantial<br>- IAB: IV in the management of otitis externa |
| CILOXAN 3 mg/ml (ciprofloxacin), ear drops in a single-dose container<br>Marketing Authorisation: 28/11/2002, amendment of 14/05/2008<br>Applicant: ALCON | "Antibacterial treatment in adults and children over the age of 1 year:<br>- acute otitis externa,<br>- purulent otorrhoea of the mastoid cavity and chronic suppurative otitis media with tympanic perforation.<br>The official guidelines on the appropriate use of antibacterials must be taken into consideration." | <u>19 October 2011</u><br>- AB: substantial<br>- IAB: IV in the management of otitis externa and V in otorrhoea |
| OFLOCET 1.5 mg/0.5 ml (ofloxacin)<br>Marketing Authorisation 1995<br>Applicant: SANOFI-AVENTIS FRANCE | - <u>In adults</u>:<br>• treatment of suppuration of the mastoid cavities,<br>• chronic suppurative otitis media with tympanic perforation.<br><u>- In children</u>:<br>Topical treatment of purulent otorrhoea:<br>- of the tympanostomy tube<br>- of the mastoid cavity<br>- of non-osteitic chronic otitis with tympanic perforation. | <u>9 October 1996</u><br>Actual Benefit:<br>substantial<br>IAB: III compared to<br>OTOFA |
| **Rifamycin antibiotic: Marketing Authorisation in otorrhoea only** | | |
| OTOFA (rifamycin 260 mg/10 ml)<br>Marketing Authorisation: 1985<br>Applicant: BOUCHARA RECORDATI | Topical treatment of some types of purulent otorrhoea:<br>• of the tympanostomy tube,<br>• of the mastoid cavity,<br>• of non-osteitic chronic otitis with tympanic perforation.<br>NB: Rifamycin is inactive against *Pseudomonas aeruginosa* with frequent clinical and microbiological failures. This pathogen is responsible for at least 30% of the infections for which this medicinal product is indicated.<br>Note: No trials has been conducted in otitis externa. | - substantial (listing renewed in 2006 and 2011) |

- **Proprietary medicinal products for topical use containing a combination of "antibiotic(s) plus corticosteroid". Preparations containing an aminoside antibiotic (neomycin, framycetin) are contraindicated in cases of perforated eardrum due to the risk of ototoxicity.**

| Proprietary medicinal product (INN) | Therapeutic indications | Committee opinion |
|---|---|---|
| **Marketing Authorisation in otitis externa with no tympanic perforation** | | |
| POLYDEXA (neomycin 1 g or 650,000 IU/100 ml + polymyxin B 1,000,000 IU/100 ml + dexamethasone 0.1 g/100 ml)<br>Marketing Authorisation: 1977<br>Applicant: BOUCHARA RECORDATI | Topical treatment of bacterial otitis externa with no tympanic perforation, in particular infected eczema of the external auditory canal.<br>**This medicine should never be used in cases of perforated eardrum due to the risk of ototoxicity.** | - moderate (class reassessment in 2000 and renewal of inclusion in 2006 and 2011) |
| CORTICETINE (framycetine 630,000 IU/100 ml + dexamethasone 0.1 g/100 ml)<br>Marketing Authorisation: 1999<br>Applicant: CHAUVIN | Topical treatment of bacterial otitis externa with no tympanic perforation, in particular infected eczema of the external auditory canal.<br>**This medicine should never be used in cases of perforated eardrum due to the risk of ototoxicity.** | - moderate (class reassessment in 2000 and renewal of inclusion in 2007) |
| FRAMYXONE (framycetin 0.7 g/100 ml + polymyxin B 700,000 IU/10 ml + dexamethasone 0.1 g/100 ml)<br>Marketing Authorisation: 1996<br>Applicant: JOLLY-JATEL | Topical treatment of bacterial otitis externa with no tympanic perforation, in particular infected eczema of the external auditory canal.<br>**This medicine should never be used in cases of perforated eardrum due to the risk of ototoxicity.** | - moderate (class reassessment in 2000 and renewal of inclusion in 2006 and 2011) |
| ANTIBIO-SYNALAR (neomycin 350,000 IU/100 ml + polymyxin B 1,000,000 IU/100 ml + fluocinolone 0.025 g/100 ml)<br>Marketing Authorisation: 1996<br>Applicant: JOLLY-JATEL | Topical treatment of bacterial otitis externa with no tympanic perforation, in particular infected eczema of the external auditory canal.<br>**This medicine should never be used in cases of perforated eardrum due to the risk of ototoxicity.** | - moderate (class reassessment in 2000 and renewal of inclusion in 2006 and 2011) |
| AURICULARUM (oxytetracycline, polymyxin B, dexamethasone, **nystatin**)<br>Marketing Authorisation: 1987<br>Applicant: GRIMBERG | Topical treatment of:<br>- bacterial and/or mycotic otitis externa;<br>- chronic otitis:<br>. - for preoperative drainage,<br>. - for postoperative use in petromastoid cavity, with or without tympanoplasty.<br>**Contraindication: dry perforation of the eardrum** | - **substantial** (inclusion of new presentation in 2005) |
| 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)<br>Marketing Authorisation: 1996<br>Applicant: ZAMBON FRANCE | Topical treatment of bacterial otitis externa with no tympanic perforation, in particular infected eczema of the external auditory canal.<br>**This medicine should never be used in cases of perforated eardrum due to the risk of ototoxicity.** | - moderate (class reassessment in 2000 and renewal of inclusion in 2006 and 2011) |

## Conclusion

**As CILOXADEX are ear drops containing a fluoroquinolone antibiotic (ciprofloxacin), the most relevant comparators are antibiotics in the same therapeutic category: CILOXAN (ciprofloxacin) and CETRAXAL (ciprofloxacin) or OFLOCET (ofloxacin). However, in contrast to these antibiotics, CILOXADEX additionally contains a corticosteroid (dexamethasone) in its composition.**

**The other comparators cited are also relevant, but they are indicated only in acute otitis externa with no tympanic perforation, except for OTOFA which has Marketing Authorisation in the treatment of purulent otorrhoea.**

# 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

**Marketing Authorisation obtained abroad (European Union, United States, Australia, Japan, Canada)**
Unites States: Marketing Authorisation in July 2003 for CIPRODEX with the same indications.
Europe: Germany, Spain, Denmark, United Kingdom, Italy by a decentralised procedure, including France.

As of the date of submission of the dossier, the medicinal product does not qualify for reimbursement by the national health insurance systems of the countries of the European Union.

# 08 SUMMARY OF PREVIOUS ASSESSMENTS

Not applicable.

# 09 ANALYSIS OF AVAILABLE DATA

The dossier is based on five clinical studies:

- **Two studies in the treatment of otitis externa with no tympanic perforation**

- a phase III study (C-98-18), comparing the efficacy and safety of ear drops containing ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CIPRODEX, equivalent to CILOXADEX) with those of ear drops containing ciprofloxacin 3 mg/ml alone (CILOXAN) or ear drops containing polymixin B sulfate 10,000 IU/ml, neomycin 3.5 mg/ml and hydrocortisone 10 mg/ml (CORTISPORIN), over a period of 7 days. This study was conducted in the USA between April 1998 and May 2000.
- a phase III study (C-98-19), comparing the efficacy and safety of ear drops containing ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CILODEX, equivalent to CILOXADEX) with those of ear drops containing polymixin B sulfate 10,000 IU/ml, neomycin 3.5 mg/ml and hydrocortisone 10 mg/ml (CORTISPORIN), over a treatment period of 7 days. This study was conducted in the USA between April 1998 and July 1999.

- **Three studies in the treatment of tympanostomy tube otorrhoea in <u>paediatric patients with associated acute otitis media.</u>**

- a phase II study (C-99-59) comparing the efficacy and safety of ear drops containing ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CIPRODEX) versus ear drops containing ciprofloxacin 3 mg/ml alone (CILOXAN), in terms of the time taken for the otorrhoea to stop. This phase II study, conducted in the USA between March 2000 and February 2001, cannot be considered relevant in the context of this assessment. Indeed, the dose of the fixed combination of ciprofloxacin 3 mg/ml + dexamethasone evaluated (three drops twice daily) does not correspond to that recommended in the French Marketing Authorisation for CILOXADEX (four drops twice daily) and the selected comparator (CILOXAN) does not have express Marketing Authorisation in this indication.
- a phase III study (C-00-52) comparing the efficacy and safety of ear drops containing ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CIPRODEX) versus ofloxacin 1.5 mg/0.5 ml, ear drops in a single-dose container (FLOXIN , equivalent to OFLOCET 1.5 mg/0.5 ml). This study was conducted in the USA and Canada between February 2001 and May 2002. However, the dose of ofloxacin (five drops twice daily) administered in this study was lower than that recommended in its French Marketing Authorisation (10 drops twice daily).
- a phase IV study (C-02-57) comparing the efficacy and safety of ear drops containing ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CIPRODEX) versus amoxicillin/clavulanic acid per os (AUGMENTIN, amoxicillin 600 mg/clavulanic acid 42.9 mg). This study was conducted in the USA between May 2003 and May 2004. It cannot be regarded as relevant in the context of this assessment owing to the choice of comparator and the small size of the

study populations included. Moreover, the amoxicillin/clavulanic acid ratio in AUGMENTIN (14:1) used as the comparator does not correspond to that of the medicinal products containing amoxicillin/clavulanic acid per os (8:1) marketed in France.

Also, only the phase III study (C-00-52) will be taken into account in the context of this assessment to estimate the effect size of the fixed combination of ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml, as ear drops, in the treatment of tympanostomy tube otorrhoea. The results of the phase II study (C-99-59) and those of the phase IV study (C-02-57) are described for purposes of illustration.

***Note:***
*- The proprietary medicinal products CIPRODEX and CILODEX assessed in the clinical studies are not marketed in France, but they are equivalent to CILOXADEX in terms of their active ingredient content (same strengths).*
*- The proprietary medicinal product CORTISPORIN, used as a comparator in acute otitis externa, is not marketed in France; however, its composition is close to that of the class of proprietary medicinal products marketed in France and composed of combinations of two antibiotics (aminoside + polypeptide) and a corticosteroid, such as POLYDEXA and PANOTILE. But it cannot be regarded as strictly equivalent to these proprietary medicinal products, given the difference in the amount of antibiotic (neomycin 10 g/ml in POLYDEXA and PANOTILE, versus 3.5 mg/ml in CORTISPORIN) and of corticosteroid.*
*- The proprietary medicinal product FLOXIN (ofloxacin) used as a comparator in tympanostomy tube otorrhoea is not marketed in France; it is however equivalent to OFLOCET 1.5 mg/0.5 ml, ear drops in a single-dose container, in terms of its active ingredient composition (identical strengths).*

# 09.1 Efficacy

## 9.1.1 Acute otitis externa

**In the single-blind (blinded from the investigator), randomised, controlled phase III study (C-98-18)**, the efficacy of the fixed combination of ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CILOXADEX) was compared to that of ciprofloxacin 3 mg/ml (CILOXAN) and a fixed combination of polymyxin B sulfate 10,000 IU/ml, neomycin 3.5 mg/ml and hydrocortisone 10 mg/ml (CORTISPORIN) over a treatment period of 7 days (children: three drops twice daily; adults: four drops twice daily).

The aim of the study was to demonstrate:

- the non-inferiority (delta threshold = 10%) of CILOXADEX compared with CILOXAN and CORTISPORIN in terms of clinical cure at the follow-up visit on D+18 days.
- the superiority of CILOXADEX compared with CILOXAN in terms of the time it took for the ear pain to stop.

On inclusion, patients had to have moderate to severe acute otitis externa, be at least one year old and exhibit the following symptoms: slight oedema, moderate inflammation and painful tenderness.

Patients with a perforated or altered tympanic membrane could not be included in the study.

A total of 909 patients, adults and children (with a mean age of around 21 years), were included in the study (CILOXADEX, n = 305, CILOXAN, n = 305 and CORTISPORIN, n = 299) and 712 were included in the PP analysis (CILOXADEX, n = 238, CILOXAN, n = 246 and CORTISPORIN, n = 228). The proportion of positive cultures was similar in all three groups (about 70%) with a predominance of *Pseudomonas aeruginosa* and *Staphylococcus aureus*, the two species most commonly encountered in this disease.

- In the per protocol (PP) analysis, the non-inferiority of CILOXADEX was demonstrated in terms of clinical cure in comparison with CILOXAN (95.4% versus 95.5%; difference -0.15%, 95% CI [-3.9; 3.6]) and CORTISPORIN (95.4% versus 91.2%, difference 4.1%, 95% CI [-0.4; 8.7]. The results of the ITT analysis (82.3% versus 82% and 81%) endorse those of the PP analysis.
- In the ITT analysis, no difference was observed between CILOXADEX and CILOXAN in the time it took for the ear pain to subside (mean: 7.1 days versus 6.7 days; median: 5 days in both

groups). The results of the PP analysis (mean: 5.7 days versus 5.5 days; median: 5 days) endorse those of the ITT analysis.

**In the single-blind (blinded from the investigator), randomised, controlled, phase III study (C-98-19)**, the efficacy of the fixed combination of ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CILOXADEX) was compared to that of a fixed combination of polymixin B sulfate 10,000 IU/ml, neomycin 3.5 mg/ml and hydrocortisone 10 mg/ml (CORTISPORIN) over a treatment period of 7 days (children: three drops twice daily; adults: four drops twice daily).

The aim of the study was to demonstrate the non-inferiority (delta threshold = 10%) of CILOXADEX compared to CORTISPORIN in terms of clinical and bacteriological cure (eradication) at the follow-up visit on D+18 days.

On inclusion, patients had to have moderate or severe acute otitis externa, be at least one year old and exhibit the following symptoms: slight oedema, moderate inflammation and painful tenderness.

Patients with a perforated or altered tympanic membrane could not be included in the study.

A total of 468 patients, adults and children (with a mean age of around 22.8 years), were included in the study (CIPRODEX, n = 232, and CORTISPORIN, n = 236) 393 were included in the PP analysis (CILOXADEX, n = 194 and CORTISPORIN, n = 199). The proportion of positive cultures was similar in the two groups (86,5%), with a predominance of *Pseudomonas aeruginosa* and *Staphylococcus aureus*, the two species most commonly found in this disease.

In the per protocol analysis, the non-inferiority of CILOXADEX versus CORTISPORIN was demonstrated in terms of:

- clinical cure (97.4% versus 93%, difference 4.5%, 95% CI [0.3; 8,6]).
- and bacteriological eradication (96.3% versus 87.9%; difference 8.4% [2.7; 14,1]).

The ITT analysis shows clinical cure percentages of 88.8% versus 83.5% (difference 5.3%, 95% CI [-0.9; 11.6] and bacteriological eradication of 94.2% versus 85.5% (difference 8.7%, 95% CI [2.5; 15,0]).

### 9.1.2 Tympanostomy tube otorrhoea

**In the single-blind (blinded from the investigator), randomised, controlled, phase III study (C-00-52)**, the efficacy of the fixed combination of ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CILOXADEX) was compared with that of ofloxacin 0.3%, ear drops, in the treatment of acute otitis media with tympanostomy tube otorrhoea. The treatment duration was 7 days for CILOXADEX (four drops twice daily) and 10 days for ofloxacin 0.3% (five drops twice daily).

The aim of the study was to demonstrate the non-inferiority (delta threshold = 10%) of CILOXADEX compared with ofloxacin in terms of clinical cure (complete disappearance of otorrhoea) and bacteriological cure (bacterial eradication) at the follow-up visit on D+18-21 days.

The inclusion criteria were: paediatric patients aged from 6 months to 12 years, with otorrhoea in the preceding 3 weeks and tympanostomy tubes for more than 3 days. No concomitant systemic antibiotic therapy or inflammatory treatment were permissible during the study. However, the use of analgesics was authorised.

A total of 599 patients (mean age 2.4 years) were included in the study (CIPRODEX, n = 297, and ofloxacin, n = 302) and 460 were included in the PP analysis (235 versus 225). The mean duration of the acute otitis media episode was approximately 4.5 days. The proportion of positive cultures was similar in the two groups (78%); the pathogens most commonly identified were: *Streptococcus pneumoniae* (16.8%), *Staphylococcus aureus* (13.0%), *Pseudomonas aeruginosa* (12.7%), *Haemophilus influenzae* (12.4%), *Staphylococcus epidermidis* (10.2%) and *Moraxella catarrhalis* (4.1%).

In the per protocol analysis, the non-inferiority of CILOXADEX versus ofloxacin was demonstrated in terms of:

- clinical cure (87.9% versus 77.3%, difference 10.7%, 95% CI [3.7; 17,6]).

- and bacteriological eradication (71.1% versus 63.2%; difference 7.9%, CI 95% [-0.7; 16,16]).

The ITT analysis shows clinical cure percentages of 74.7% versus 61.3% (difference 13.5%, 95% CI [6.1; 20.9] and bacteriological eradication of 56.9% versus 49.0% (difference 7.9%, 95% CI [-0.07; 15.9]). In patients with a positive culture on inclusion, the bacteriological eradication percentages were 91.7% versus 81.8% (difference 9.9% [2.8; 16.9] in the PP analysis and 80.3% versus 66.7% (difference 13.6%, 95% CI [5.3; 21.9] in the ITT analysis.

**In the single-blind (blinded from the investigator), randomised, controlled, phase II study (C-99-59)**, the efficacy of the fixed combination of ciprofloxacin 3 mg/ml + dexamethasone 1 mg/ml (CILOXADEX) was compared with that of ciprofloxacin 3 mg/ml (CILOXAN) in the treatment of acute otitis media with tympanostomy tube otorrhoea. The treatment duration was 7 days for CILOXADEX (three drops twice daily) and CILOXAN (three drops twice daily).

The aim of the study was to demonstrate the superiority of CILOXADEX compared with CILOXAN in terms of the time taken to stop the otorrhoea.

A total of 201 patients were recruited into the study, with ages from 6 months to 12 years (mean age 2.4 years). Of these patients, 192 (100 in the CILOXADEX group versus 92 in the CILOXAN group were included in the ITT analysis, and 171 (89 versus 82) in the PP analysis.

The results of this study (ITT analysis) show a shorter mean time taken for the otorrhoea to stop (primary efficacy endpoint) in the CILOXADEX group (mean 4.1 days, median 4 days) than in the CILOXAN group (mean 5.4 days, median 5 days), i.e. a mean difference of 1 day ($p < 0.001$). This difference in the effect size is clinically of little relevance.

**In the single-blind (blinded from the investigator), randomised, controlled, phase IV study (C-02-57)**, the efficacy of the fixed combination of ciprofloxacin + dexamethasone (CILOXADEX) was compared with that of an oral suspension of amoxicillin 600 mg/clavulanic acid 42.9 mg (AUGMENTIN) in the treatment of acute otitis media with tympanostomy tube otorrhoea. The treatment duration was 7 days for CILOXADEX (four drops twice daily) and 10 days for AUGMENTIN (90 mg/kg/day in two doses 12 hours apart).

The aim of the study was to describe the efficacy of CILOXADEX in comparison with AUGMENTIN 600 mg in terms of the time taken to stop the otorrhoea and to achieve a clinical cure at the follow-up visit on Day D+18.

A total of 80 patients were recruited and included in the ITT analysis (39 in the CILOXADEX group versus 41 in the AUGMENTIN group), with ages from 6 months to 12 years (mean age 1.9 years). Of these patients, 66 (34 versus 32) were included in the PP analysis.

The results of this study show:

- a shorter mean time taken for the otorrhoea to stop in the CILOXADEX group (mean 4.9 days, median 4 days) than in the AUGMENTIN group (mean 8.7 days, median 7 days), i.e. a mean difference of 3 days ($p < 0.001$) in the ITT analysis. This result is confirmed by the PP analysis.
- in terms of clinical cure, a difference between the two treatments in the ITT analysis (84.6% versus 58.5%; $p = 0.01$) and not in the PP analysis (88% versus 70%).

## 09.2 Adverse effects

In the various clinical studies the treatment was well tolerated, with a frequency of adverse effects (< 5%) similar to that of the topical antibiotics used as comparators.
In the phase III clinical studies carried out in otitis externa, pruritus was the adverse effect most commonly observed (study C-98-18: 1.3% in the CILOXADEX group versus 1.3% in the CILOXAN and CORTISPORIN groups; study C-98-19: 1.3% versus 4.7% in the CORTISPORIN group).
In the phase III clinical study (C-00-52) versus ofloxacin 1.5 mg/0.5 ml, ear drops, conducted in patients with tympanostomy tube otorrhoea, the most commonly observed adverse effects were a burning sensation in the ear (3.4% versus 1%) and ear pain (2.4% versus 3%).

Reports on clinical experience with the use of the ciprofloxacin + dexamethasone ear drops (medicinal product available in the USA since 2003) have not revealed any major concerns as regards safety of use of this antibiotic.

**Summary of the safety profile according to the SPC**
"In five clinical studies involving 976 patients, CILOXADEX was administered twice daily. Three studies included 439 patients with tympanostomy tube otorrhoea and two studies included 537 patients with acute otitis externa. No serious otic or systemic CILOXADEX-related adverse effects were reported in any of these clinical studies.

Tabulated summary of adverse effects
The following adverse reactions listed in the table below were observed during clinical studies or since being placed on the market. They are ranked according to system organ class and classified according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), or not known (cannot be estimated from the available data).

| System organ classification | Frequency | Adverse effects |
|---|---|---|
| **Infections and infestations** | Uncommon | Candidiasis, fungal ear infection |
| **Nervous system disorders** | Common | Dysgeusia |
| | Uncommon | Paraesthesia (tingling in ears), dizziness, headache, crying |
| **Ear and labyrinth disorders** | Common | Ear pain, ear discomfort, ear pruritus |
| | Uncommon | Hypoacusis, tinnitus, otorrhoea, ear congestion |
| **Vascular disorders** | Uncommon | Flushing |
| **Gastrointestinal disorders** | Uncommon | Vomiting |
| **Skin and subcutaneous tissue disorders** | Uncommon | Skin exfoliation, erythematous rash |
| **General disorders and administration site conditions** | Uncommon | Irritability, fatigue |
| **Investigations** | Uncommon | Medication residue |
| **Injury, poisoning and procedural complications** | Uncommon | Device occlusion (tympanostomy tube obstruction) |

Description of selected adverse effects
The most frequently reported adverse effects reported in the 439 patients with tympanostomy tube otorrhoea were ear pain (2.5%), ear discomfort (2.5%), and dysgeusia (defined as the taste of the medicine) (1.1%). Only 1 patient discontinued therapy due to an adverse effect, namely ear discomfort.
The most frequently reported adverse effect reported in the 537 patients with acute otitis externa was ear pruritus (1.5%). No patients were forced to stop the treatment on that account.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angiooedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria and itching.
Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability were reported in patients receiving systemic fluoroquinolones. Studies and postmarketing experience with systemic fluoroquinolones indicate that the risk of these ruptures may be increased in patients receiving corticosteroids (especially elderly patients) and in tendons under high stress (including the Achilles tendon). To date, clinical and postmarketing data have not demonstrated any clear association between otic administration of ciprofloxacin and these musculoskeletal and connective tissue adverse effects.

Paediatric population
CILOXADEX was shown to be safe in children 6 months of age or older for the treatment of tympanic tube otorrhoea and in children aged 1 year or older for the treatment of acute otitis externa. The frequency, type and severity of adverse effects in paediatric patients are expected to be the same as in adults."

Special warnings and precautions for use (see Section 4.4 of the SPC)
Attention is drawn to the risk of local skin reactions and irritation due to the presence of benzalkonium chloride.
**A warning was added, pointing out that corticosteroids can diminish immune response and thus promote the occurrence of bacterial, viral and fungal infections. They can mask the clinical signs of an infection, precluding any possibility of detecting inefficacy in the antibiotic; they can also suppress hypersensitivity reactions to substances present in the medicinal product.**

## 09.3 Summary & discussion

- **Acute otitis externa**

Two randomised studies were conducted in single-blind mode (studies C-98-18 and C-98-19) in patients at least one year old (mean 22 months) and suffering from otitis externa with no tympanic perforation. The fixed ciprofloxacin/dexamethasone combination (CILOXADEX) was non-inferior (delta threshold = 10%) to ciprofloxacin alone (CILOXAN) or to a fixed aminoside/polypeptide/corticosteroid combination (CORTISPORIN), with clinical and bacteriological cure percentages greater than 90% after 7 days of treatment. No difference was observed between CILOXADEX and CILOXAN in the time taken to stop the ear pain (mean: 7.1 days versus 6.7 days; median: 5 days).

- **Tympanostomy tube otorrhoea**

A randomised study was conducted in single-blind mode (study C-00-52), in patients aged from 6 months to 12 years (mean 2.4 years) with acute otitis media and tympanostomy tube otorrhoea. The fixed ciprofloxacin/dexamethasone combination (four drops twice daily for 7 days) was non-inferior to ofloxacin 0.3% (five drops twice daily for 10 days). In the PP analysis, the percentage clinical cure was 87.9% versus 77.3% (difference 10.7%, 95% CI [3.7; 17.6] and the percentage bacteriological eradication was 71.1% versus 63.2% (difference 7.9%, 95% CI [-0.7; 16.16]). However, the dose of ofloxacin (five drops twice daily) administered in this study is lower than that in its French Marketing Authorisation (10 drops twice daily); this limits the transferability of the results of this study to French practice. In the absence of a group treated with ciprofloxacin alone, it is impossible with this study to estimate the added value of dexamethasone on the efficacy observed with the fixed ciprofloxacin/dexamethasone combination (CILOXADEX).
A randomised phase II study compared, in single-blind mode (study C-99-59), the fixed ciprofloxacin/dexamethasone combination (three drops twice daily) with ciprofloxacin (three drops twice daily) for 7 days. The mean time taken for the otorrhoea to stop was shorter with the fixed ciprofloxacin/dexamethasone combination than with ciprofloxacin (4.1 versus 5.4 days; $p < 0.001$), but this difference is of little clinical relevance.

➢ **Safety**

Overall, the treatment was well tolerated in the clinical studies. No serious CILOXADEX-related otic or systemic adverse effects were reported in any of the clinical studies.

A warning was added in the SPC, pointing out that corticosteroids can diminish immune response and thus promote the occurrence of bacterial, viral and fungal infections. They can mask the clinical signs of an infection, precluding any possibility of detecting inefficacy in the antibiotic; they can also suppress hypersensitivity reactions to substances present in the medicinal product (see Section 4.4 of the SPC).

## 09.4 Programme of studies

Not applicable.

# 010 THERAPEUTIC USE

- In acute otitis externa, topical antibiotic therapy relies for a first-line treatment on the use of the fluoroquinolone class of antibiotics (ciprofloxacin, ofloxacin) or of a preparation containing aminosides, except in cases of perforated eardrum on account of the risk of ototoxicity. Of all the fluoroquinolones, only ciprofloxacin (CILOXAN or CETRAXAL) has Marketing Authorisation specifically in this indication. CILOXADEX (fixed combination of ciprofloxacin + dexamethasone) is a new treatment option to using ciprofloxacin by itself. However, the clinical benefit of dexamethasone has not been demonstrated in relation to the use of ciprofloxacin alone.

- In patients with tympanostomy tube otorrhoea, first-line topical antibiotic therapy relies on fluoroquinolone (ciprofloxacin or ofloxacin). Rifamycin (OTOFA) also has Marketing Authorisation in this indication, but it is inactive against *Pseudomonas aeruginosa*, with frequent clinical and microbiological failures. CILOXADEX (fixed ciprofloxacin/dexamethasone combination) is a new treatment alternative to using ciprofloxacin alone or ofloxacin. The addition of dexamethasone to an antibiotic could make for faster drainage of the otorrhoea than by using the topical antibiotic on its own;[3] however, the benefit of such an effect has yet to be established, and a corticosteroid-related risk (decreased immune response, masking of the clinical signs of infection) cannot be ruled out.

[3] Schmelzle J, Birtwhistle RV, Tan AK. Acute otitis media in children with tympanostomy tubes. *Can fam Physician.* 2008; 54 (8): 1123-7

# 011 TRANSPARENCY COMMITTEE CONCLUSIONS

**In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:**

## 011.1 Actual benefit

◗ Acute otitis externa and purulent otorrhoea of bacterial origin do not present the usual serious character but can entail debilitating complications with a risk of deafness.

◗ CILOXADEX, ear drops, is accepted as a curative treatment for acute otitis externa and tympanostomy tube otorrhoea.

◗ It is a first-line treatment.

◗ The efficacy/adverse effects ratio of CILOXADEX is moderate, given the lack of any demonstrable potential clinical benefit for the corticosteroid (dexamethasone) in the combination.

◗ There are treatment alternatives.

◗ Expected public health benefit

In public health terms, the burden represented by bacterial otitis externa is small, despite its frequency, in the absence of habitual severity. They do nevertheless lead to countless visits to the doctor and school absenteeism. In addition, the burden represented by tympanostomy tube otorrhoea is small.

The management of bacterial otitis is not one of the established public health priorities.

In light of the available clinical trial data [in particular non-inferiority versus ciprofloxacin alone and CORTISPORIN in cases of acute otitis externa, and also versus ofloxacin (at a lower dose than that given in the Marketing Authorisation) in cases of tympanostomy tube otorrhoea], CILOXADEX is not expected to have any additional impact on morbidity in these indications.

No impact on the organisation of healthcare is expected.

Consequently, it is not expected that the medicinal product CILOXADEX will benefit public health in these indications.

**Taking account of these points, the Committee considers that the actual benefit of CILOXADEX is moderate in the Marketing Authorisation indications.**

## 011.2 Improvement in actual benefit (IAB)

CILOXADEX does not offer any improvement in actual benefit (IAB V, nonexistent) compared with topical antibiotics for auricular use belonging to the fluoroquinolone class of antibiotics (antibiotic alone without corticosteroid: ciprofloxacin or ofloxacin) currently on the market in the management of acute otitis externa and tympanostomy tube otorrhoea.

## 011.3 Target population

According to data from the General Medical Observatory (in 2009), otitis externa accounts for around 1% of doctor's visits in general practice. In 2009, every GP saw an average of 13.2 patients for 15.1 procedures in the otitis externa indication[4].

If these figures are set against the total number of general practitioners (101,896 in 2012),[5] the number of consultations for otitis externa in general practice may be estimated at around 1,500,000. This figure does not take account of consultations with specialists (ENT and paediatricians). Besides, it is not possible from the data to estimate the frequency with which antibiotics are prescribed during consultations for acute otitis externa or tympanostomy tube otorrhoea.

# 012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

**The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation.**

- **Proposed reimbursement rate: 30%**

- **Packaging:** Appropriate for the prescription conditions

[4] Observatoire de la Médecine Générale (General Medical Observatory): Informations épidémiologiques sur les pathologies et leur prise en charge en ville. http://omg.sfmg.org/

[5] INSEE (French national institute of statistics and economic studies): Professions de santé. Available at: http://insee.fr/fr/themes/tableau.asp?ref_id=NATTEF06103 (consulted on 09/04/2013)