

Medicines Adverse Reactions Committee

Meeting date	8 June 2017	Agenda item	3.2.1
Title	Safety of Antibiotic Ear Drops in children with Grommets		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent(s)	Medicines		Sponsors
Clioquinol; Flumetasone pivalate	Locorten-Vioform Locacorten-Viaform		AFT Pharmaceuticals
Ciprofloxacin; Hydrocortisone	Ciproxin HC Otic Ear drops		Pharmaco (NZ) Ltd
Framycetin; Gramicidin; Dexamethasone	Sofradex		Sanofi-aventis New Zealand limited
Framycetin	Soframycin		Sanofi-aventis New Zealand limited
Neomycin; Gramicidin; Nystatin; Triamcinolone	Kenacomb Ear drops		Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Funding	Locorten-Vioform/Locacorten-Viaform; Kenacomb; Sofradex*; Soframycin*. *Part funded only		
Previous MARC meetings	None		
International action	None		
Prescriber Update	None		
Schedule	Prescription		
Advice sought	<p>The Committee is asked to advise whether:</p> <ul style="list-style-type: none"> – there is evidence of a difference in the risk of ototoxicity between the antibiotic containing ear drops when used in children with grommets or in patients with a perforated tympanic membrane – the sponsor for Ciproxin HC (quinolone) ear drops should be given the opportunity to remove the contraindication for use in patients with a perforated tympanic membrane and replace it with a warning statement – the sponsor for Locorten-Vioform/Locacorten-Viaform (hydroxyquinolone) include information on the risk of ototoxicity – the sponsors for Sofradex, Soframycin and Kenacomb (aminoglycosides) should add a warning statement indicating that the risk of ototoxicity is increased with increasing duration of use and continuation of treatment after resolution of symptoms – this safety concern requires further communication other than MARC's Remarks in <i>Prescriber Update</i>. 		

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1.0 PURPOSE

The purpose of this report is to review the safety of using antibiotic containing ear drops in children with grommets.

2.0 BACKGROUND

In November 2015, CARM informed Medsafe of a case report of Locorten-Vioform use in a child with grommets. As the Locorten-Vioform data sheet contraindicates use in patients with a perforated ear drum, an assessment of the safety of using ear drops in children with grommets was considered necessary.

CARM indicated that Lareb had presented a series of similar cases at the National Pharmacovigilance Centres Meeting in October 2015. Lareb presented 34 reports of possible ototoxicity (dizziness, impaired hearing) in association with ear drops containing colistimethate, bacitracin and hydrocortisone, which are indicated for use in otitis externa in the Netherlands. Fifteen reports indicated that they had been used in people with non-intact tympanic membranes. Lareb expressed concern that these ear drops were being used despite the contraindication in the data sheets. However, they acknowledged that the ear drops may have been used off-label to treat chronic suppurative otitis media (CSOM), which could confound the reports as CSOM is a known cause of ototoxicity.

Medsafe comment

There are no ear drops containing colistimethate or bacitracin with consent for distribution in New Zealand. As no details of individual cases are provided in the Lareb abstract, it is unclear how many (if any) patients had grommets, how long they were treated for, whether symptoms improved when treatment was stopped and whether long term follow-up has occurred.

Colistimethate is a polymyxin antibiotic which is a class of antibiotics which has been associated with ototoxicity in published case reports (See below). NZ guidelines advise against the use of polymyxin containing ear drops except upon the advice of an ear nose and throat ENT specialist (1).

2.1 Antibiotic Containing Ear Drops

There is a range of antibiotic and combination antibiotic/corticosteroid containing ear drops available for use in New Zealand (Table 1). Most of the approved products contain an aminoglycoside antibiotic (such as framycetin, gramicidin and neomycin). Locorten-Vioform contains clioquinol, which is a hydroxyquinolone compound that has broad-spectrum antimicrobial activity against fungi and gram-positive bacteria and has a moderate inhibitory effect on gram-negative bacteria (2). Currently, there is only one available product containing a quinolone antibiotic (Ciproxin). However, there is another consented product that contains a quinolone antibiotic (Cilodex) that is currently not available. PHARMAC does not currently fund any ear drops containing quinolone antibiotics (Table 1).

All products are indicated for the treatment of otitis externa (Table 1). All data sheets, including those containing quinolone antibiotics, contraindicate use in the presence of a perforated tympanic membrane. None of the available data sheets of ear drops containing antibiotics include information regarding use in children with grommets.

Table 1: Ear drops approved for use in New Zealand

Brand name and ingredient	Indications	Use with perforated tympanic membrane and/or grommets	Warning statements
Locacorten-Viaform and Locorten-Vioform (Annex 1) <i>(Clioquinol, Flumetasone pivalate)</i> Hydroxyquinolone antibiotic FUNDED BY PHARMAC	Eczema of the external auditory meatus in which secondary infection with micro-organisms sensitive to clioquinol has occurred. Otitis externa Otomycosis	Contraindications Perforation of the ear-drum (suspected or verified) <i>No reference to use in grommets.</i>	Contraindications Use in children under 2 years of age. Special warnings and special precautions for use Prior to the beginning of therapy, the ear-drum should be checked by the physician. If there is a risk that perforation of the ear-drum may occur or is perforated, LOCACORTEN-VIAFORM® ear drops should not be used
Ciproxin HC Otic Ear drops (Annex 2) <i>(Ciprofloxacin 0.2%, Hydrocortisone 1%)</i> Quinolone antibiotic	The treatment of acute bacterial external otitis caused by organisms susceptible to the action of ciprofloxacin, including <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Acinetobacter anitratus</i> (<i>baumannii</i>), <i>Stenotrophomonas maltophilia</i> , <i>Enterobacteriaceae</i> , <i>Enterococcus faecalis</i> and <i>Proteus mirabilis</i> .	Contraindications The safety and efficacy of Ciproxin HC Ear Drops have not been studied in the presence of a perforated tympanic membrane. Ciproxin HC Ear Drops are, therefore, contraindicated in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane. <i>No reference to grommets.</i>	None
Sofradex (Annex 3) <i>(Framycetin, Gramicidin, Dexamethasone)</i> Aminoglycoside antibiotic FUNDED BY PHARMAC	In the ear: Otitis externa.	Contraindications Otitis externa should not be treated when the eardrum is perforated because of the risk of ototoxicity. <i>No reference to grommets.</i>	Warnings and Precautions Aminoglycoside antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment. Although this effect has not been reported following topical ocular use, the possibility should be considered when high dose topical treatment is given to small children or infants.
Soframycin (Annex 4) <i>(Framycetin)</i>	Otitis externa.	Contraindications Perforation of the tympanic membrane	Warnings and Precautions

Aminoglycoside antibiotic FUNDED BY PHARMAC		<i>No reference to grommets.</i>	Aminoglycoside antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment. Although this effect has not been reported following topical ocular use, the possibility should be considered when high dose topical treatment is given to small children or infants.
Kenacomb (Annex 5) (<i>Gramicidin, Neomycin, Nystatin, Triamcinolone acetonide</i>) Aminoglycoside antibiotic FUNDED BY PHARMAC	The topical treatment of superficial bacterial infections, cutaneous candidosis and dermatological conditions known to respond to topical steroid therapy when threatened or complicated by bacterial or candidal superinfections, especially otitis externa.	Contraindications Should not be applied to the external auditory canal in patients with perforated eardrums. <i>No reference to grommets.</i>	Special warnings and precautions for use Care is necessary in applying this preparation if perforation of the eardrum is suspected. Because of the potential hazard of nephrotoxicity and ototoxicity, this medication should not be used in patients with extensive skin damage or other conditions where absorption of neomycin is possible.
Cilodex Ear Drops (<i>Ciprofloxacin 0.33%, Dexamethasone 1%</i>) Quinolone antibiotic	Cilodex is indicated for the topical treatment of acute otitis media in patients with tympanostomy tubes and acute otitis externa in patients caused by strains of bacteria susceptible to ciprofloxacin.	No data sheet as not currently available	No data sheet as not currently available

2.2 Otorrhoea

2.2.1 Acute tympanostomy tube otorrhoea

Grommets (also known as tympanostomy or ventilation tubes) are used to restore hearing in children with chronic otitis media (inflammation of the middle ear) with effusion (OME) and can also be used to prevent recurrent OME. Insertion of grommets is one of the most common day ENT surgeries performed in children (3, 4).



Source: www.kidshealth.org.nz

Figure 1: Grommet *in situ*

Acute otorrhoea (or discharge from the ear) is common following grommet insertion (5). It can be accompanied by an unpleasant odour, pain and fever which can negatively affect a child's quality of life. It is estimated that between 25 % and 75 % of children will develop otorrhoea at some point post-surgery, although not all cases will be symptomatic (3, 4, 6). In 4 % of children chronic suppurative otitis media (CSOM) will develop and otorrhoea will become persistent (4).

Acute tympanostomy tube otorrhoea is thought to be caused by bacterial infection of the middle ear (acute otitis media). Therefore, treatment is aimed at eradicating the infection (5).

2.2.2 Otitis Externa

Otitis externa is an inflammatory reaction of the lining of the ear canal usually associated with an underlying seborrhoeic dermatitis or eczema (1). It usually presents with itchiness, pain and/or otorrhoea. Many cases recover after thorough cleansing of the external ear canal by suction or dry mopping. However, corticosteroid containing ear drops may also be required. Secondary bacterial or fungal infection can occur, particularly after prolonged topical treatment of otitis externa.

Otitis externa is less common in children than in adults (1).

2.2.3 Chronic Suppurative Otitis Media (CSOM)

CSOM causes recurrent or persistent otorrhoea through a perforation in the tympanic membrane, and can lead to thickening of the middle-ear mucosa and mucosal polyps (7). It usually occurs as a complication of persistent acute otitis media with perforation in childhood. CSOM is associated with a risk of progressive hearing loss if the infection and discharge persists.

2.3 Comparison with International Data Sheets

A selection of product information from other regulators is presented in Table 2.

Table 2: Australian, UK, Canadian and USA information on risk of ototoxicity and warnings/contraindications for use in a perforated tympanic membrane or grommets

Product Name	Australia	United Kingdom	Canada	USA
Locacorten-Viaform Ear Drops	<p>Amdipharm Mercury (Australia) Pty Ltd, Nov 2016</p> <p>Contraindications Perforation of the ear-drum (suspected or verified)</p> <p>Precautions Prior to the beginning of therapy, the ear-drum should be examined by the physician. If there is a risk that perforation of the ear-drum may occur, Locacorten-Vioform ear drops should not be used.</p>	<p>Amdipharm UK Limited, Nov 2013</p> <p>Contraindications Perforation of the tympanic membrane</p>	<p>Paladin Labs Inc. May 2009</p> <p>Contraindications Perforation of the ear-drum (suspected or verified)</p> <p>Precautions Prior to the beginning of therapy, the eardrum should be examined by the physician. Locacorten-Vioform ear drops should not be used if there is a risk that perforation of the ear-drum may occur or has occurred.</p>	N/A
Ciproxin HC Ear Drops (Aus)	<p>Ciproxin HC Alcon, Inc. by Bayer HealthCare AG, Mar 2014</p> <p>Contraindications The safety and efficacy of CIPROXIN HC Ear Drops have not been studied in the presence of a perforated tympanic membrane. CIPROXIN HC Ear Drops are, therefore, contraindicated in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane.</p>	<p>Cilodex (<i>1 ml of suspension contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone</i>) Alcon Laboratories (UK) Limited, Mar 2015</p> <p>Therapeutic indication CILODEX is indicated for the treatment of the following infections in adults and children (see section 4.2). See section 5.1 for commonly susceptible species.</p> <ul style="list-style-type: none"> • Acute otitis media in patients with tympanostomy tubes (AOMT) • Acute otitis externa (AOE) 	<p>Ciprodex (<i>Ciprofloxacin /Dexamethasone 0.3% w/v (as ciprofloxacin hydrochloride)/ 0.1% w/v</i>) Novartis Pharmaceuticals Canada Inc. Feb 2017</p> <p>Indications and Usage CIPRODEX is indicated for the treatment of infections caused by most strains of the designated microorganisms in the specific conditions listed below:</p> <p>Acute Otitis Media with Otorrhea through tympanostomy tubes in pediatric patients, ≥ 6 months of age</p>	<p>Cetraxal (<i>Ciprofloxacin 0.2%</i>) Ciprofloxacin Otis (<i>Ciprofloxacin 0.2%</i>) No contraindication or warnings</p> <p>Ciprodex (<i>ciprofloxacin hydrochloride 0.3 % and dexamethasone 0.1 %</i>) Alcon Laboratories, Inc, Aug 2016</p> <p>Indications Ciprodex is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below: Acute Otitis Media in pediatric patients (age 6 months and older) with tympanostomy tubes</p>
Sofradex (Aus)	<p>Sanofi-aventis Australia Pty Ltd, Jan 2010</p> <p>Contraindications Perforation of tympanic membrane.</p>	<p>Sanofi-aventis, Mar 2017</p> <p>Contraindications Otitis Externa should not be treated when the eardrum is perforated because of the risk of ototoxicity</p>	N/A	N/A

Product Name	Australia	United Kingdom	Canada	USA
	No warning that may cause deafness when applied topically.	<p>Warnings</p> <p>Aminoglycosides antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment. Although this effect has not been reported following ocular use, the possibility should be considered when high dose topical is given to small children or infants.</p>		
Soframycin (Aus)	<p>Sanofi-aventis Australia Pty Ltd, Feb 2009</p> <p>Contraindications</p> <p>Perforation of the tympanic membrane.</p> <p>No warning that may cause deafness when applied topically.</p>	N/A	N/A	N/A
Kenacomb (Aus) Otosporin (UK)	<p>Kenacomb (Neomycin; Triamcinolone acetonide; Nystatin; Gramicidin) Aspen Pharma Pty Ltd, Nov 2013</p> <p>Contraindications</p> <p>In the treatment of otitis media or in the presence of a perforate tympanic membrane.</p>	<p>Otosporin (Polymyxin B Sulphate; Neomycin Sulphate; Hydrocortisone) Phoenix Labs, Mar 2015</p> <p>Contraindications</p> <p>The use of Otosporin Ear Drops is contra-indicated in patients in whom perforation of the tympanic membrane is known or suspected.</p>	N/A	<p>Neomycin/polymyxin B sulfates/hydrocortisone suspension/drops Numerous companies</p> <p>Warnings</p> <p>Neomycin and polymyxin B sulfates and hydrocortisone otic suspension should not be used in any patient with a perforated tympanic membrane.</p> <p>OR</p> <p>Due to its acidity which may cause burning and stinging, neomycin and polymyxin B sulfates and hydrocortisone otic solution should not be used in any patients with a perforated tympanic membrane.</p>

Medsafe Comment

Cilodex (ciprofloxacin/dexamethasone) is approved in New Zealand for the topical treatment of acute otitis media in patients with tympanostomy tubes but is currently not available.

Ciloquin (ciprofloxacin 0.3%) and Ciloxan (ciprofloxacin 0.3%) are both approved for use in Australia and are not contraindicated in patients with a perforated ear drum and contain no warnings. They both include “Published studies in paediatric and adult patients with a tympanic perforation (artificial or natural), showed minimal systemic absorption of ciprofloxacin following ototopical administration.”

In the US, Ofloxacin Otic (0.3% ofloxacin) is approved for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

- *Otitis Externa in adults and pediatric patients, 6 months and older, due to Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus.*
- *Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to Proteus mirabilis, Pseudomonas aeruginosa, and Staphylococcus aureus.*
- *Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus pneumoniae.*

3.0 CLINICAL GUIDELINES

3.1 New Zealand

3.1.1 BPAC

BPAC advises that topical quinolones should be used as the first line treatment for chronic suppurative otitis media (CSOM) in children with grommets, due to the small risk of ototoxicity associated with the use of non-quinolone topical antibiotics such as aminoglycosides (4). BPAC advises that ciprofloxacin with hydrocortisone ear drops are effective in treating CSOM but are not subsidised.

To allow the ear drops to better penetrate affected tissues, the external auditory canal should be cleaned using suction prior to administration. Children who fail to respond to topical antibiotics should be referred for more intensive treatment.

3.1.2 New Zealand Formulary and New Zealand Formulary for Children

The New Zealand Formulary (NZF) advises that in view of reports of ototoxicity, manufacturers contraindicate topical treatment with ototoxic antibacterials in the presence of a tympanic perforation or patent grommet. However, the NZF indicates that many ENT specialists use potentially ototoxic antibacterial ear drops (ie, those containing aminoglycosides or polymyxins) cautiously in children (and adults) with perforated tympanic membranes of grommets. They can be used as first line treatment of CSOM (as the benefits of rapid resolution of otitis media are considered to outweigh the theoretic risks associated with topical therapy); and when other measures have failed for the treatment of otitis externa.

The NZF indicates that aminoglycoside or polymyxin containing ear drops should only be used by ENT specialists, and in the following circumstances:

- drops should only be used in the presence of obvious infection
- treatment should be for no longer than two weeks
- the carer and child should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics
- baseline audiology should be performed, if practical, before treatment is commenced.

The NZF advises that ciprofloxacin with hydrocortisone ear drops are an effective alternative to aminoglycoside containing ear drops for chronic otitis media in patients with perforation of the tympanic membrane but highlights that this is an unapproved indication.

3.1.3 New Zealand Society of Otolaryngology Head and Neck Surgery (NZSOHNS)(8)

A position statement on the use of eardrops with ototoxic potential in the presence of tympanic membrane perforation, ventilation tubes and mastoid cavities with open middle ear was issued in 2007.

The following specific advice was given.

- It is preferable to use non ototoxic drops in the presence of tympanic membrane perforation, ventilation tubes and mastoid cavities with open middle ear.
- If potentially ototoxic eardrops are used then they should be used only in the presence of infection and should be discontinued immediately after infection has resolved. The treatment should preferably be limited to a maximum of two weeks.
- If potentially ototoxic eardrops are prescribed for the treatment of ear infection with either a tympanic membrane perforation, ventilation tube or open middle ear/mastoid cavity, then the reason for use and the potential ototoxicity should be discussed with the patient/parent and documented (risk 1:1000 to 1:10000).
- If potentially ototoxic drops are prescribed, then the patient should be advised to return to the doctors if vertigo, hearing loss or tinnitus develop during or soon after treatment.
- Use of potentially ototoxic eardrops is acceptable in the presence of an intact tympanic membrane.

The Society accepts that potentially ototoxic agents may need to be used in certain circumstances (eg, lack of therapeutic response to other agents, resistant organisms, non-availability, or non-affordability of non-ototoxic agents). In these situations, potentially ototoxic drops may reasonably be used, but treatment should be limited to the period when the ear is actually discharging.

Medsafe comment

Recent correspondence from the NZSOHNS dated 10 February 2017 indicates that this position has not changed. The Society is continuing to request that PHARMAC fully subsidise a ciprofloxacin containing ear drop from PHARMAC due to a lower risk of ototoxicity.

3.1.4 Kids Health

This website provides general information on grommets for the general public and advises that ear discharge following grommet insertion is usually treated with ear drops (www.kidshealth.org.nz/grommets-tympanostomy-or-ventilation-tubes).

Medsafe comment

New Zealand guidelines recommend the use of antibiotic ear drops as first line treatment for grommet associated otorrhoea. Quinolone antibiotics are recommended over aminoglycoside containing ear drops but their use is limited by the lack of funding for quinolone containing ear drops in New Zealand.

No specific advice is given regarding the use of Locorten-Vioform ear drops.

3.2 International Guidelines

3.2.1 Australia

In 2007, the Consensus Panel of the Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS) produced guidance based on a systematic review of the literature and expert consensus (9). The advice offered was consistent with that issued by the NZ Society of Otolaryngology Head and Neck Surgery in the same year.

General practitioner guidance on the management of external ear conditions published in 2007 recommended that quinolone containing ear drops should be used to treat otitis externa if tympanic membrane perforation is known or suspected (10). It also advised that Locacorten-Viaform should be used with caution to treat fungal otitis externa or diffuse acute otitis externa in the presence of a tympanic membrane perforation.

3.2.2 UK

A position statement issued by ENT UK in 2007, based on a systematic literature review and clinical consensus, recommended the following treatment of patients with a discharging ear, in whom there is a perforation or patent grommet (11).

- If a topical aminoglycoside is used, this should only be in the presence of obvious infection.
- Topical aminoglycosides should be used for no longer than two weeks.
- The justification for using topical aminoglycosides should be explained to the patient.
- Baseline audiology should be performed, if possible or practical, before treatment with topical aminoglycosides.

Medsafe comment

At the time this guideline was developed, no ear drops containing quinolone antibiotics were approved for use in the UK.

3.2.3 Canada

Evidence based guidelines produced in 2008 recommended that topical fluoroquinolones, with or without a corticosteroid, should be the treatment of choice for acute otitis media with tympanostomy tubes (AOMT) (12). The authors indicated that this recommendation was based on strong evidence that topical treatment with fluoroquinolones, with or without the addition of corticosteroids, is more effective than systemic antibiotics at resolving AOMT and results in less antibiotic resistance and fewer adverse effects, including ototoxicity, than other treatments do. The review recommended that topical aminoglycoside agents should not be used due to the potential for rare ototoxicity.

3.2.4 USA

Evidence based guidelines produced by the American Academy of Otolaryngology in 2013, produced a strong recommendation that acute, uncomplicated, tympanostomy tube otorrhoea should be treated with topical antibiotic eardrops only, without oral antibiotics (13). This recommendation was based on strong evidence that topical antibiotic eardrops are safer than oral antibiotics with equal efficacy.

Medsafe comment

This recommendation was based on review of three randomised controlled trials (RCTs) comparing topical antibiotic ear drops to systemic antibiotics. All three RCTs used quinolone antibiotics.

3.3 Other Guidelines

3.3.1 UpToDate 2016

In 2016, the UpToDate group in the US (who provide evidence based physician authored clinical decision support resources) produced guidance recommending that uncomplicated tympanostomy tube otorrhea should be treated with topical antibiotic ear drops with or without corticosteroids. They also advised:

- the use of corticosteroid-containing fluoroquinolone drops where available (eg, ciprofloxacin and dexamethasone otic suspension, four drops into the affected ear twice daily for five days) is recommended
- oral or parenteral antibiotics should be reserved for children with a concurrent infection (eg, sinusitis, streptococcal pharyngitis, adjacent auricular cellulitis), blocked external auditory canal, or who are immunocompromised.

This recommendation was graded 2B by the authors. A grade 2 recommendation is a weak recommendation which suggests that the benefits and risks are finely balanced and/or uncertain. B grade evidence indicates moderate quality evidence from either randomised trials with important limitations, or very strong evidence from other sorts of trials (eg, observational studies).

Medsafe comment

International guidelines are consistent with New Zealand guidelines and recommend the use of antibiotic containing ear drops as first line treatment for tympanostomy tube otorrhoea. Quinolone containing ear drops are preferred over aminoglycoside or polymyxin containing ear drops due to a lower risk of ototoxicity. The UK and Australian guidelines include clear advice on the safe use of potentially ototoxic ear drops which is consistent with advice issued by the New Zealand Society of Otolaryngology Head and Neck Surgery in 2007 and the NZF in 2016.

These guidelines have been produced using robust evidence based review methodologies which include a systematic review of the available literature and expert consensus. However, the evidence used to inform these guidelines is limited by a paucity of high quality primary studies. In particular, there is a paucity of directly relevant clinical studies which evaluated the safety and efficacy of the antibiotic and antibiotic/corticosteroid combinations contained in the ear drops available for use in New Zealand.

4.0 SCIENTIFIC INFORMATION

4.1 Systematic Reviews

4.1.1 Venekemp *et al.* 2016 (6)

This Cochrane systematic review included evidence up to June 2016. Nine randomised controlled trials (RCTs), enrolling 2,132 children were included. The objective of the review was to compare the safety and efficacy of antibiotic eardrops (with or without corticosteroid) to oral antibiotics in children with ear discharge following grommet insertion. The individual studies were judged to have low to moderate risk of bias.

As seen in Table 3, there was moderate to low-quality evidence that antibiotic eardrops (with or without corticosteroid) are more effective than oral antibiotics, corticosteroid eardrops and no treatment in children with ear discharge occurring at least two weeks following grommet insertion. There is some limited, inconclusive evidence that antibiotic eardrops are more effective than saline rinsing. There is uncertainty whether antibiotic-corticosteroid eardrops are more effective than eardrops containing antibiotics only.

Medsafe comment

This was a high quality systematic review. However, it was limited by the small numbers of primary studies and limited types of antibiotic containing ear drops included in individual studies. Most studies included either ciprofloxacin, ofloxacin or bacitracin-colistin-hydrocortisone. Therefore, are not directly relevant to the funded antibiotic containing ear drops available for use in New Zealand.

Table 3: Antibiotic ear drops (with or without corticosteroid) versus oral antibiotics for children with grommets who develop ear discharge beyond the immediate postoperative period.

Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics for children with grommets (ventilation tubes) who develop ear discharge beyond the immediate postoperative period						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	n [#] of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral antibiotics	Risk with antibiotic eardrops				
Resolution of ear discharge at short-term follow-up (1 week)	Study population	RR 2.58 (1.27 to 5.22)	42 (1 RCT)	⊕⊕⊕○ moderate ¹	The NNTB based on the study population risk was $1/(774-381)*1000 = 2.55$	-
	300 per 1000 (381 to 1000)	774 per 1000 (381 to 1000)				
Adverse events	Study population	RR 0.37 (0.12 to 1.09)	705 (3 RCTs)	⊕⊕○○ low ²	-	-
	317 per 1000 (38 to 345)	117 per 1000 (38 to 345)				
Serious complications	Study population	n/a	153 (1 RCT)	⊕○○○ very low ³	-	-
	0 per 1000 (0 to 0)	0 per 1000 (0 to 0)				
Resolution of ear discharge at intermediate-term follow-up (2 weeks)	Study population	RR 1.70 (1.38 to 2.08)	153 (1 RCT)	⊕⊕⊕○ moderate ⁴	-	-
	558 per 1000 (771 to 1000)	949 per 1000 (771 to 1000)				
Duration of ear discharge	Antibiotic eardrops versus oral antibiotics: Median 4 days (range 1 to 28) versus 5 days (range 1 to 36) Median 4 days (range not reported) versus 7 days (range not reported)	n/a	232 (2 RCTs)	⊕⊕⊕○ moderate ⁴	-	-
Tube blockage	Study population	RR 1.20 (0.33 to 4.45)	121 (2 RCTs)	⊕⊕○○ low ⁵	-	-
	50 per 1000 (17 to 223)	60 per 1000 (17 to 223)				
Health-related quality of life						
Generic - CHQ	At 2 weeks, the change in CHQ scores did not differ significantly between the groups. The change in Otitis Media-6 total score (range 6 to 42) at 2 weeks was small but favoured antibiotic-corticosteroid eardrops (difference in median difference between treatment groups: -2, P < 0.01)	n/a	153 (1 RCT)	⊕⊕○○ low ⁶	-	-
Disease-specific - OM-6 (range 6 to 42)	Change in median score: +1 (baseline: 15.5; 2 weeks: 16.5) Change in median score: -1 (baseline: 15.5; 2 weeks: 14.5)	Difference in change in median OM-6 scores: -2 (1 RCT) (in favour of antibiotic eardrops)	153 (1 RCT)	⊕⊕○○ low ⁶	-	-

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
 CHQ: Child Health Questionnaire; CI: confidence interval; n/a: not applicable; NNTB: number needed to treat to benefit; OM-6: Otitis Media-6; RCT: randomised controlled trial;
 RR: risk ratio

4.1.2 Harris et al. 2016 (14)

This systematic review of RCTs compared the efficacy of topical aminoglycosides with topical quinolones in the treatment of chronic suppurative otitis media. Nine trials met the inclusion criteria. Two studies showed a higher clinical cure rate in the quinolone group (93 % v. 71 %, p = 0.04, and 76 % v. 52 %, p = 0.009). Four studies showed no statistically significant difference in clinical outcome.

The authors concluded that topical quinolones have equal or superior efficacy to topical aminoglycosides for the treatment of CSOM and the prevention of infection post myringotomy.

4.1.3 Chee et al. 2016 (3)

A systematic review identified four RCTs comparing the efficacy of topical and oral antibiotics for the treatment of otorrhoea in children (aged <12 years) with tympanostomy tubes (grommets). This review demonstrated that topical treatments had better cure (Number needed to benefit [NNTB] = 4.7, pooled RR = 1.35, p < 0.001) and microbiological eradication (NNTB = 3.5, pooled RR = 1.47 95% CI, p < 0.001 among 3 of the studies) than oral antibiotics. Oral antibiotics had higher risk of diarrhoea (pooled RR = 21.5, 95% CI 8.00–58.0, p < 0.001, NNTH = 5.4) and dermatitis (pooled RR = 3.14, 95% CI 1.20–8.20, p = 0.019, NNTH = 32). The use of topical steroids in addition to topical antibiotics was associated with a higher cure rate (pooled RR = 1.59, p < 0.001 vs. pooled RR = 1.57, p = 0.293).

The authors concluded that ototopical therapy should be the first choice in the treatment of acute tube otorrhoea in view of its excellent cure rates and microbiological eradication coupled with a safe side effect profile.

Medsafe Comment

The published literature confirms the efficacy of topical antibiotic ear drops, compared to systemic antibiotics, and topical quinolone antibiotics compared to topical aminoglycosides, to treat CSOM or post tympanostomy otorrhoea. No studies of clioquinol were included in this review.

4.1.4 Matz et al. 2004 (15)

The authors systematically reviewed 14 articles evaluating hearing loss or vestibular changes after the use of ototoxic ear drops. Most included studies were uncontrolled cohort studies or case series. 54 cases of vestibular toxicity (including 24 which also had evidence of auditory toxicity) associated with gentamicin ear drops were identified. The majority of reports occurred in the second week of treatment. Eleven reports of auditory toxicity and two reports of vestibular toxicity associated with topical neomycin/polymyxin B based ear drops were also identified. No reports of ototoxicity were identified when aminoglycoside ear drops were used to treat otitis externa in the presence of an intact tympanic membrane.

Three studies evaluating the risk of ototoxicity in children with grommets were identified.

- Rakover et al. (1997) reviewed 358 children with grommets who received polymyxin ear drops for two weeks. No changes in hearing were identified three months later.
- Merifield et al. (1993) treated children with either polymyxin B, neomycin, or gentamicin ear drops for up to eight days and also noted no change in auditory threshold in patients treated with tympanostomy tubes.
- Welling et al. (1995) evaluated the use of polymyxin or neomycin drops after a single dose and reported no auditory toxicity.

However, six case reports of ototoxicity when gentamicin ear drops were used in patients with ventilation tubes were identified. Vestibular toxicity did not occur before day one and in some cases didn't occur until 16 weeks after treatment.

The authors concluded the following:

- neomycin/polymyxin ear drops are safe when used in patients with tympanostomy tubes provided they are used for a short period of time (level 1 b evidence from two papers)
- gentamicin ear drops can cause vestibular toxicity when used in patients with a perforated tympanic membrane for longer periods of time (level 3 b evidence from one paper)
- if polymyxin B, neomycin, or gentamicin drops were used for prolonged periods of time, that is, longer than two weeks in patients with tympanic membrane perforations or open mastoid cavities, patients should be warned of the risk of either vestibular or cochlear toxicity. The use of ototopical drops should be discontinued if the patient reports symptoms associated with vestibular/cochlear toxicity
- there is no evidence that monitoring reduces toxicity.

The authors suggested that cases of unilateral vestibular toxicity may go unrecognised and unreported due to compensatory central mechanisms.

4.2 Clinical Information

4.2.1 Mahadevan *et al.* 2008 (16)

In 2007, New Zealand ENT specialists were surveyed to determine their prescribing preferences for antibiotic containing ear drops (16). Both Sofradex and Ciproxin HC ear drops were prescribed most often by ENT specialists for discharging ears in the presence of grommets and tympanic membrane perforations. A potential risk of ototoxicity and the cost to patients affected the choice of antibiotic ear drop prescribed.

Respondents reported 24 cases of hearing loss that were at least possibly related to the use of antibiotic ear drops. Sofradex (framycetin) was most commonly implicated (16 cases). No reports of ototoxicity with the use of quinolone antibiotic ear drops were reported. However, two reports of hearing loss with Locorten-Vioform ear drops were identified.

The authors recommended that non-ototoxic topical fluoroquinolones be used in preference to potentially ototoxic topical aminoglycosides in clinical situations where ototoxicity is a concern (eg, if there is a non-intact tympanic membrane and either pre-existing sensorineural hearing loss is present; prolonged otopical medication is required; or if there is a family or personal history of sensitivity to aminoglycosides).

Medsafe comment

Evidence from case reports suggests that vestibular and auditory toxicity can occur with aminoglycoside and polymyxin antibiotic ear drops. The risk appears to be increased with increasing duration of use. Two reports of hearing loss with clioquinol containing ear drops were identified in New Zealand, although no details were available for assessment.

4.3 CARM Data

There have been two reports of ototoxicity/hearing impaired reported to the Centre for Adverse Reactions Monitoring (CARM) (Annex 11).

1. 084638: impaired hearing reported in a female patient following use of Kenacomb ear drops.
2. 090599: ototoxicity reported in a 46-year-old male in association with Sofradex.

4.4 Usage Data

The usage data of PHARMAC funded antibiotic containing ear drops indicates that Sofradex, Locorten-Vioform and Kenacomb are being used in the New Zealand setting (Annex 12). However, it is unknown the indications that these antibiotic ear drops were used for.

The New Zealand guidelines and the New Zealand survey by Mahadevan *et al.* would also suggest that Ciproxin HC is used in New Zealand even though it is not currently funded (16).

5.0 DISCUSSION AND CONCLUSIONS

Currently in New Zealand, none of the antibiotic containing ear drops available for use are approved for the treatment of CSOM, post tympanostomy associated otorrhoea, or otitis externa in the presence of a perforated tympanic membrane or patent tympanostomy tube (grommet). Therefore, all usage of ear drops for these indications is considered off-label treatment in New Zealand. In addition, all the currently available antibiotic containing ear drops are contraindicated in patients with either suspected or confirmed perforations of the ear drum. There is one antibiotic containing ear drop approved and indicated for treatment of acute otitis media with tympanostomy tubes and acute otitis externa (Cilodex: ciprofloxacin and dexamethasone) that is currently not available in New Zealand.

New Zealand and international guidelines recommend the use of antibiotic containing ear drops as first line treatment of CSOM and tympanostomy associated otorrhoea. This recommendation is based on evidence of equivalent or superior efficacy to systemic antibiotics, and a superior safety profile. Quinolone containing ear drops are recommended over those containing aminoglycosides or polymyxins. This is reflected in the approval in the UK and Medsafe of a quinolone containing ear drop (ciprofloxacin) for use in the presence of a tympanostomy tube and the approval in the US of a quinolone containing ear drop (ofloxacin) for use in the presence of a tympanostomy tube or in the case of a perforated tympanic membrane. In addition, ciprofloxacin containing ear drops without corticosteroids are approved for use in Australia with no contraindication or warning regarding use in patients with perforation of the tympanic membrane. However, both the Australian and New Zealand product Ciproxin, which contains a quinolone and a corticosteroid (ciprofloxacin/hydrocortisone), are contraindicated in patients with perforation of the ear drum.

In New Zealand, PHARMAC does not fund any quinolone containing ear drop (with or without a corticosteroid). Therefore, it is likely that the hydroxyquinolone containing ear drop (Locorten-Vioform) and/or aminoglycoside containing ear drops (Sofradex, Soframycin, Kenacomb) are being used preferentially in New Zealand. The usage data would support this although it is impossible to know to what extent Ciproxin is being used.

The most serious safety concern associated with the use of ear drops in the presence of a perforated tympanic membrane or a patent tympanostomy tube (grommet) is the potential for ototoxicity (hearing or balance changes) to occur. Data from case reports suggests that ototoxicity is a rare complication of treatment with ear drops containing aminoglycoside or polymyxin containing ear drops (risk 1:1000 to 1:10000). However, case reports may be confounded by the presence of chronic suppurative otitis media which can also cause ototoxicity. There is some evidence that ototoxicity is more likely if ear drops are continued after active infection is resolved and/or if they are used for more than 1-2 weeks. The available evidence suggests that ciprofloxacin (and clioquinol) containing ear drops are associated with a significantly lower risk of ototoxicity.

The available evidence from clinical studies and expert opinions, suggest that antibiotic containing ear drops are an effective treatment for CSOM and/or tympanostomy associated otorrhoea and can be used safely in the presence of a perforated tympanic membrane and/or a patent tympanostomy tube. Quinolone containing ear drops should be used first line due to evidence of equivalent efficacy, and a lower risk of ototoxicity than aminoglycoside containing ear drops. Due to a paucity of data, the relative safety and efficacy of clioquinol containing ear drops compared to other antibiotic ear drops is unknown.

The warning statements regarding the risk of ototoxicity in antibiotic containing ear drops differs between the medicines. The quinolone (Ciproxin) and hydroxyquinolone (Locorten-Vioform) do not contain any warning/information on ototoxicity. Whereas the aminoglycosides, Sofradex and Soframycin, include information that aminoglycoside antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. Sofradex and Soframycin also state that this effect has not been reported following topical ocular use but that it is possible particularly when high dose topical treatment is given to children. The aminoglycoside antibiotic containing ear drop, Kenacomb, contains a warning that care is necessary in applying this preparation if perforation of the eardrum is suspected and because of the potential hazard of nephrotoxicity and ototoxicity, this medication should not be used in patients with extensive skin damage or other conditions where absorption of neomycin is possible.

Based on this review, there is no evidence to suggest that Ciproxin HC should be contraindicated for use in children with a perforated tympanic membrane or those with grommets. However, all data sheets require more detailed information on the risk of ototoxicity occurring.

NB: that subclinical vestibular toxicity may occur but not be evident due to compensatory mechanisms.

6.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- there is evidence of a difference in the risk of ototoxicity between the antibiotic containing ear drops when used in children with grommets or in patients with a perforated tympanic membrane
- the sponsor for Ciproxin HC (quinolone) ear drops should be given the opportunity to remove the contraindication for use in patients with a perforated tympanic membrane and replace it with a warning statement
- the sponsor for Locorten-Vioform/Locacorten-Viaform (hydroxyquinolone) include information on the risk of ototoxicity
- the sponsors for Sofradex, Soframycin and Kenacomb (aminoglycosides) should add a warning statement indicating that the risk of ototoxicity is increased with increasing duration of use and continuation of treatment after resolution of symptoms
- this safety concern requires further communication other than MARC's Remarks in *Prescriber Update*.

7.0 ANNEXES

1. AFT Pharmaceuticals Ltd. 2016. *Locorten-Vioform data sheet* September 2016.
2. Pharmaco (NZ) Ltd. 2014. *Ciproxin data sheet* July 2014.
3. Sanofi-Aventis New Zealand Limited. 2009. *Sofradex data sheet* 19 February 2009.
4. Sanofi-Aventis New Zealand Limited. 2009. *Soframycin data sheet* 16 February 2009.
5. Pharmacy Rtailing (NZ) Limited. 2017. *Kenacomb data sheet* 7 March 2017.
6. Venekamp RP, Javed F, van Dongen T, et al. 2016. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. *Cochrane Library of Systematic Reviews*.
7. Harris A, Elhassan H, Flook E. 2016. Why are ototopical aminoglycosides still first-line therapy for chronic suppurative otitis media? A systematic review and discussion of aminoglycosides versus quinolones. *The Journal of Laryngology & Otology* 130: 2–7.
8. Chee J, Pang KW, Yong JM, et al. 2016. Topical versus oral antibiotics, with or without corticosteroids, in the treatment of tympanostomy tube otorrhea. *International Journal of Pediatric Otorhinolaryngology* 86: 183–8.
9. Matz G, Rybak L, Roland PS, et al. 2004. Ototoxicity of ototopical antibiotic drops in humans. *Otolaryngology—Head and Neck Surgery* 130: S79–S82.
10. Mahadevan M, Wabnitz DA, McIntosh DL, et al. 2008. Survey on the use of ototopical medications by New Zealand otolaryngologist/head and neck surgeons. *The New Zealand Medical Journal (Online)* 121.
11. CARM data
12. PHARMAC usage data

8.0 REFERENCES

1. New Zealand Formulary. *Drugs Acting on the Ear NZF*.
2. AFT Pharmaceuticals Ltd. 2016. *Locorten Vioform data sheet*. September 2016.
3. Chee J, Pang KW, Yong JM, et al. 2016. Topical versus oral antibiotics, with or without corticosteroids, in the treatment of tympanostomy tube otorrhea. *International Journal of Pediatric Otorhinolaryngology* 86: 183-8.
4. Best Practice Advocacy Centre. 2012. Otitis media: a common childhood illness *Best Practice Journal* 46: 25-9.
5. van Dongen TM, van der Heijden GJ, Venekamp RP, et al. 2014. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *New England Journal of Medicine* 370: 723-33.
6. Venekamp RP, Javed F, van Dongen T, et al. 2016. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. *Cochrane Library of Systematic Reviews*.
7. Morris P. 2012. Chronic suppurative otitis media. *BMJ clinical evidence* 2012.
8. Gilbert JG, Dawes PJ, Mahadevan M, et al. 2007. Use of ototoxic eardrops: a position statement from the New Zealand Society of Otolaryngology Head and Neck Surgery. *New Zealand Medical Journal* 120: 84-5.
9. Black RJ, Cousins VC, Chapman P, et al. 2007. Ototoxic ear drops with grommet and tympanic membrane perforations: a position statement. *Medical Journal of Australia* 186: 605.
10. Taplin M. 2007. How to treat external ear conditions. *Australian Doctor* 25-32.
11. Phillips J, Yung M, Burton M, et al. 2007. Evidence review and ENT-UK consensus report for the use of aminoglycoside-containing ear drops in the presence of an open middle ear. *Clinical Otolaryngology* 32: 330-6.
12. Schmelzle J, Birtwhistle RV, Tan AK. 2008. Acute otitis media in children with tympanostomy tubes. *Canadian Family Physician* 54: 1123-7.
13. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. 2013. Clinical practice guideline: Tympanostomy tubes in children. *Otolaryngol Head Neck Surgery* 149: S1-35.
14. Harris A, Elhassan H, Flook E. 2016. Why are ototopical aminoglycosides still first-line therapy for chronic suppurative otitis media? A systematic review and discussion of aminoglycosides versus quinolones. *The Journal of Laryngology & Otology* 130: 2-7.
15. Matz G, Rybak L, Roland PS, et al. 2004. Ototoxicity of ototopical antibiotic drops in humans. *Otolaryngology--Head and Neck Surgery* 130: S79-S82.
16. Mahadevan M, Wabnitz DA, McIntosh DL, et al. 2008. Survey on the use of ototopical medications by New Zealand otolaryngologist/head and neck surgeons. *The New Zealand Medical Journal (Online)* 121.