## Medicines Adverse Reactions Committee

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| Meeting date | 13/03/2025 | Agenda item | 3.2.1 |
| Title | **Systemic fluoroquinolones: update on regulatory actions and review of safety concerns** | | |
| Submitted by | Medsafe Pharmacovigilance Team | Paper type | For advice |

| **Active ingredient** | **Product name** | **Sponsor** |
|---|---|---|
| Ciprofloxacin | Ipca-Ciprofloxacin tablet | Ipca Pharma |
| | Aspen Ciprofloxacin injection | Pharmacy Retailing |
| Moxifloxacin | Avelox tablet, infusion | Bayer |
| | Moxifloxacin Kabi injection | Fresenium Kabi |
| Norfloxacin | Arrow-Norfloxacin tablet | Teva Pharma |

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| PHARMAC funding | Ipca-Ciprofloxacin, Avelox (special authority), Arrow-Norfloxacin (endorsement) |
| Previous MARC meetings | Fluoroquinolones and aortic aneurysm or dissection June 2019<br>Assessment of the potential risk of disabling and persistent musculoskeletal and nervous system adverse reactions from the use of fluoroquinolones December 2017 |
| International action | MHRA: Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects<br>EMA: Dear Healthcare Professional Communication- Systemic and inhaled fluoroquinolone antibiotics- reminder on restrictions of use<br>See section 2.2 for additional regulatory action. |
| *Prescriber Update* | Drug-induced tendinopathy (September 2024)<br>Reports of persisting serious adverse reactions to fluoroquinolones (September 2023)<br>Aortic aneurysm/dissection- The Achilles heel of fluoroquinolones (December 2019)<br>Quinolones- A Tendoncy to Rupture (September 2012) |
| Classification | Prescription medicine |
| Usage data | See section 2.1.3 |
| Advice sought | **The Committee is asked to advise:**<br>• Due to the risk of prolonged, disabling and potentially persistent serious reactions, do the indications of fluoroquinolones need to be modified to reserve use for severe infections in order to maintain a favourable benefit-risk profile?<br>• Whether the data sheets for fluoroquinolones need to be updated to further highlight the risk of prolonged, disabling and potentially persistent (or irreversible) serious adverse reactions and/or other safety concerns?<br>• This topic requires further communication other than MARC's Remarks in *Prescriber Update*? |

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# 1 PURPOSE

Fluoroquinolone antibiotics have been associated with prolonged, disabling and potentially persistent and/or irreversible adverse reactions that may affect multiple body systems, and include musculoskeletal, nervous, psychiatric, and sensory reactions. These reactions have been reported in patients irrespective of their age and potential risk factors, and there are no proven treatments available. The frequency of these reactions is usually considered to be rare or unknown.

Due to the risk of serious persisting adverse reactions, several regulatory agencies have restricted the indications for use of fluoroquinolone antibiotics. The most recent action was taken by the MHRA in January 2024. The MHRA recommended that fluoroquinolones must only be used when other antibiotics that are commonly recommended for the infection are inappropriate, an addition to the 2019 restrictions where fluoroquinolones should not be prescribed in non-severe, self-limiting, or non-bacterial conditions [1].

This paper provides an update on regulatory actions regarding the risk of disabling and persistent adverse drug reactions in relation to treatment with fluoroquinolones. The possibility of restricting indications for fluoroquinolones was previously discussed in the December 2017 and June 2019 MARC meetings.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) have also requested the product information of fluoroquinolone antibiotics be updated with information on DRESS syndrome. Currently the majority of fluoroquinolone data sheets do not list DRESS as an adverse drug reaction.

Following the safety concerns described above and recent actions taken by international regulatory agencies, Medsafe is requesting advice from the MARC on whether the restrictions to the indications for use of fluoroquinolone antibiotics are needed, and/or if any updates to the data sheet are required.

# 2 BACKGROUND

## 2.1 Fluoroquinolones

Fluoroquinolone antibiotics are used for a range of infections. They are primarily active against gram-negative bacteria, but newer generation fluoroquinolones have a broader spectrum of activity and cover some gram-positive bacteria [2]. The bactericidal action of fluoroquinolones results from the inhibition of DNA gyrase and topoisomerase IV. These enzymes are essential for the replication, repair, and transcription of bacterial DNA [3, 4].

Quinolones are active against aerobic Gram-negative bacilli and cocci, including *Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria gonorrhoeae* . They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae* [2].

Fluoroquinolones currently available in New Zealand include ciprofloxacin, moxifloxacin and norfloxacin.

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| **Comment:** This report covers systemic fluoroquinolone antibiotics. Preparations for ocular and auricular use have been excluded. |

### 2.1.1 Indications

Table 1 lists the approved indications for ciprofloxacin, moxifloxacin and norfloxacin in NZ.

**Table 1. Therapeutic indications for fluoroquinolones in NZ [3-6]**

| Fluoroquinolones | Indications |
|---|---|
| Ciprofloxacin | Adults: Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens: |

| | |
|---|---|
| | • Infections of the lower respiratory tract.<br>  • In treatment of outpatients with pneumonia due to Pneumococcus, ciprofloxacin should not be used as a medicine of first choice. Ciprofloxacin can be regarded as a suitable treatment for pneumonias caused by *Klebsiella, Enterobacter, Proteus, E.coli, Pseudomonas, Haemophilus, Branhamella, Legionella,* and *Staphylococcus*.<br>• Infections of the kidneys and/or efferent urinary tract.<br>• Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis.<br>• Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis).<br>• Infections of the skin and soft tissue<br>• Infections of the bones and joints<br>• Sepsis<br>  • Inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolised *Bacillus anthracis*. Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.<br><br>Children:<br><br>• Treatment of acute pulmonary exacerbations of cystic fibrosis associated with *P. aeruginosa* infection in patients aged 5-17-years.<br>• Inhalational anthrax (post-exposure)<br>  • Complicated urinary tract infections or pyelonephritis due to *E.coli* in patients aged 1-17 years.<br><br>The risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints/surrounding tissues. The use of ciprofloxacin for other indications is not recommended in children.<br><br>Parenteral treatment is indicated for hospitalised adult patients in whom oral ciprofloxacin is indicated but cannot be administered, or where the oral form is inappropriate.<br><br>  • Treatment of serious or life-threatening infections due to sensitive organisms involving the following organ systems: lower respiratory tract infections (gram-negative organisms), skin and skin structure, septicaemia, bone and joint, urinary tract.<br>• Inhalational anthrax (post-exposure) |
| Moxifloxacin | Tablets and solution for infusion are indicated for the treatment of the following bacterial infections caused by susceptible strains:<br><br>• Bronchitis (acute exacerbations of chronic bronchitis)<br>  • Pneumonia (community acquired)<br>• Sinusitis (acute)<br>• Complicated skin and skin structure infections (including diabetic foot infections) |

| | |
|---|---|
| | • Complicated intra-abdominal infections including polymicrobial infections such as abscesses<br><br>Tablets are indicated for the treatment of the following bacterial infections caused by susceptible strains:<br><br>• Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis)<br><br>Consideration should be given to available official guidance on the appropriate use of antibacterial agents. |
| Norfloxacin | Norfloxacin is a broad-spectrum bactericidal agent indicated for treatment of:<br><br>• Upper and lower, complicated, and uncomplicated acute urinary tract infections including cystitis, pyelitis, cystopyelitis, pyelonephritis, chronic prostatitis, epididymitis, and those urinary infections associated with urologic surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to norfloxacin.<br>• Acute bacterial gastroenteritis caused by susceptible organisms<br>• Gonococcal urethritis pharyngitis, proctitis or cervicitis caused by both penicillinase and non-penicillinase producing *Neisseria gonorrhoeae*.<br><br>Infections caused by multiple resistant organisms have been successfully treated with the usual doses of norfloxacin. |

### 2.1.2 Funding

Ipca-Ciprofloxacin is currently funded under PHARMAC's Community Schedule, where it is recommended for patients with any of the following:

- Microbiologically confirmed and clinically significant pseudomonas infection; or
- Prostatitis; or
- Pyelonephritis; or
- Gonorrhoea.

Avelox (moxifloxacin) tablets are funded via **Special Authority**. The initial application must be from:

- A respiratory or infectious disease specialist for patients with tuberculosis (with specific criteria) or mycobacterium avium-intracellular complex disease; or
    - A sexual health specialist or practitioner for mycoplasma genitalium

Arrow-Norfloxacin is funded for patients with an uncomplicated urinary tract infection (UTI) that is unresponsive to a first line agent or with proven resistance to first line agents and the prescription is **endorsed** accordingly.

**Comment:** The use of moxifloxacin for patients with tuberculosis or mycobacterium avium-intracellular disease is an unapproved indication.

### 2.1.3 Usage data

Usage data for oral fluoroquinolones dispensed in the community is shown in Table 2.

**Table 2. Number of fluoroquinolone dispensings and number of people receiving a dispensing at least once per year.**

| Year | Ciprofloxacin | | Moxifloxacin | | Norfloxacin | |
|---|---|---|---|---|---|---|
| | Dispensings | Nb of people | Dispensings | Nb of people | Dispensings | Nb of people |
| 2019 | 62,064 | 48,738 | 451 | 285 | 8,061 | 6,067 |
| 2020 | 50,565 | 38,660 | 407 | 235 | 6,540 | 4,779 |
| 2021 | 44,906 | 34,316 | 444 | 234 | 5,097 | 3,690 |
| 2022 | 43,333 | 33,511 | 495 | 234 | 3,975 | 2,837 |
| 2023 | 43,207 | 33,898 | 392 | 227 | 3,123 | 2,163 |

Source: Te Whatu Ora Pharmaceutical Data Web Tool (accessed 29 January 2025)

**Comment:** Community dispensing data indicates that the use of all fluoroquinolones is decreasing. This is not unexpected given the use of fluoroquinolones is associated with increasing antimicrobial resistance, and NZ antibiotic guidelines recommend limiting their use for specific indications.

The Pharmaceutical Web Tool does not capture usage data of medicines in the hospital setting. However, prescribing of fluoroquinolones in hospitals is generally restricted, requiring input from specialist clinicians (eg infectious disease).

### 2.1.4 Safety concerns associated with fluoroquinolones

Warnings/safety concerns for medicines are included in section 4.4 of the product information. The information below contains a summary of the warnings and precautions for use of moxifloxacin. It was taken from the Avelox (moxifloxacin) UK SPC [7]. There are some product specific concerns, but generally, the safety information should be consistent across for the class of fluoroquinolones.

Prolonged, disabling, and potentially irreversible serious adverse drug reactions:

Systemic fluoroquinolone antibiotics are associated with prolonged, disabling and potentially irreversible serious adverse drug reactions. These reactions can affect different (and sometimes multiple) body systems including musculoskeletal, nervous, psychiatric, and sensory. Reactions have been reported in patients irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling adverse reactions with fluoroquinolones. Fluoroquinolones should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber.

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions:

Fluroquinolones have been shown to prolong the QTc interval in some patients. Women may be more sensitive to QTc-prolonging medicines and elderly patients may also be more susceptible to drug-associated effects on the QT interval. Caution should be taken when prescribing fluoroquinolones in patients with proarrhythmic conditions, or medicines that reduce potassium and/or prolong the QT interval.

Hypersensitivity/allergic reactions:

Hypersensitivity and allergic reactions have been reported with fluoroquinolones, anaphylactic reactions can progress to life-threating shock.

Liver disorders:

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus or tender abdomen), treatment should be discontinued.

Severe cutaneous adverse reactions (moxifloxacin only):

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia (DRESS) which could be life-threatening or fatal have been reported.

Patients predisposed to seizures:

Quinolones are known to trigger seizures and should be used with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold.

Peripheral neuropathy:

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients should be advised to inform their doctor if symptoms of neuropathy occur in order to prevent the development of potentially irreversible condition.

Psychiatric reactions:

Psychiatric reactions may occur even after the first administration of quinolones. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts. Caution is recommended in patients with psychosis or a history of psychiatric disease.

Antibiotic-associated diarrhoea including colitis:

Antibiotic-associated diarrhoea and colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of broad-spectrum antibiotics including fluoroquinolones and may range in severity from mild diarrhoea to fatal colitis.

Patients with myasthenia gravis:

Fluoroquinolones may exacerbate symptoms of myasthenia gravis.

Tendinitis and tendon rupture:

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones, and have been reported to occur even up to several months after discontinuation of treatment.

The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with fluoroquinolones should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence:

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart

valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing:

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behç et´ s disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren´s syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

Vision disorder:

Fluoroquinolones may impair vision (transient loss of vision) especially in the course of a CNS reaction.

Hypo/hyper-glycaemia:

Disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with fluoroquinolones. Hypoglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Photosensitivity reactions:

Quinolones have been shown to cause photosensitivity reactions in patients. Patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment.

G6PD deficiency and haemolytic reactions:

Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with fluoroquinolones.

Other considerations:

Additional warnings are general recommendations and include use in patients with renal impairment, use in specific conditions (eg pelvic inflammatory disease, MRSA infections), and resistance information.

**Comment:** The product information (also known as the data sheet, SmPC, SPC) contains information on the known safety concerns of a medicine. Globally, the product information should be relatively consistent although local deviations may occur.

The Avelox UK SPC was selected as the reference as it has been updated with the MHRA recommendations (discussed below) and Avelox is the innovator product. Compared to the New Zealand information, the UK SPC contains more information on some safety concerns. Section 2.3 of this report provides a comparison of the international and New Zealand data sheets.

See Section 3.3 for a summary of adverse reactions to fluoroquinolones reported in New Zealand.

### 2.1.5 Resistance

There is a strong relationship between antibiotic consumption and antibiotic resistance. Resistance to fluoroquinolones has increased over time, both globally and in New Zealand [8, 9].

*Fletcher-Lartey et al, 2019, Trends in antimicrobial resistance patterns in Neisseria gonorrhoeae in Australia and New Zealand: A meta-analysis and systematic review [10]*

The authors conduced a meta-analysis to estimate the change in susceptibility patterns among antibiotics under surveillance in Australia and New Zealand. 29 articles published in these countries from 1980-2018 were reviewed.

Ciprofloxacin data was available in 19 studies. In Australia, the proportion of isolates susceptible to ciprofloxacin decreased over time (OR 0.90; 95%CI 0.87–0.92), with an average susceptibility of 86.4% (95%CI 79.6%–91.3%). In New Zealand a greater decrease in ciprofloxacin susceptibility was detected (OR: 0.80; 95% CI 0.68–0.93) and higher rates of resistance (OR 1.17; 95% CI 1.13–1.21) were observed in New Zealand over time.

The New Zealand, Microbiology Network publish antibiograms highlighting bacterial susceptibility to different antimicrobials. Several antibiograms are available and can be separated via region of testing, community, or hospital results and by microorganism type. The most recent data covers the 2023 susceptibility results. Table 3 presents the cumulative 2023 antibiogram for antibiotic susceptibilities in the community setting.

**Table 3: 2023 Community cumulative antibiotic susceptibilities**

**2023 Community cumulative antibiotic susceptibilities (antibiogram)**
**(Compiled January 2024, based on 2023 annual data)**

**Numbers denote % susceptible**

| | | Common usage (1st line) antibioics | | | | | | | | | | (2nd line) antibiotics | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Organism group** | Number tested | Penicillin | Amoxicillin | Amoxicillin+clavulanate | Flucloxacillin | Cephalexin | Erythromycin | Co-trimoxazole | Doxycycline | Trimethoprim* | Nitrofurantoin* | Number tested | Clindamycin | Ciprofloxacin |
| **Non urinary sites** | | | | | | | | | | | | | | |
| *Staphylococcus aureus* | 11020 | | | S^ | 90^ | S^ | 89 | 99 | 98 | | | 24# | 71 | |
| Methicillin-resistant *S. aureus* (MRSA) | 1044 | R | R | R | R | R | 82 | 99 | 98 | | | 8# | 75 | |
| *Streptococcus pyogenes* | 52 | 100 | S | S | S | S | 98 | | | | | 52 | 100 | |
| *Sreptococcus pneumoniae* | 105 | 88 | 88 | | | | 76 | 71 | 78 | | | | | |
| *Haemophilus influenzae* | 682 | | 69 | 89 | | | | 75 | 99 | | | | | |
| *Pseudomonas aeruginosa* | 332 | R | R | R | R | R | R | R | R | | | 332 | | 86 |
| **Urine isolates** | | | | | | | | | | | | | | |
| *E. coli* | 12057 | R | 57 | 87 | R | 93 | | | | 77 | 99 | 12057 | | 91 |
| ESBL-positive *E. coli* | 509 | R | R | | R | R | | 48 | | 31 | 97 | 509 | | 43 |
| *Klebsiella* spp | 1349 | R | R | 89 | R | 91 | | | | 83 | 80 | 1346 | | 93 |
| ESBL-positive *Klebsiella* spp | 75 | R | R | | R | R | | 5 | | 5 | 47 | 73 | | 48 |
| *Proteus mirabilis* | 551 | R | 89 | 98 | R | 99 | | | | 80 | | | | |
| ESCPPM§ Enterobacterales | 153 | R | R | R | R | R | | 93 | | 88 | 40 | 151 | | 98 |
| *Pseudomonas aeruginosa* | 294 | R | R | R | R | R | | R | | R | R | 294 | | 90 |
| *Enterococcus* spp | | | S | S | R | R | | | | | S | | | |
| *Staphylococcus saprophyticus* | 645 | | | S^ | S^ | S^ | | | | 92 | 99 | | | |

*Uncomplicated UTI isolates only
^ *Staphylococcus* species that are flucloxacillin susceptible can be considered susceptible to amoxycillin-clavulanate, cephazolin, cephalexin, cefaclor, and cefuroxime.
# **Caution** needed in interpreting these results as low number of isolates and testing usually performed on multi-resistant isolates.
**S** = Not specifically tested but known to be ordinarily susceptible
**R** = intrinsically resistant
§ = *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii* family, *Providencia* spp., *Proteus* spp. (excluding *P. mirabilis*), *Morganella morganii*, *Yersinia enterocolitica*

*Source: The New Zealand Microbiology Network (accessed 28 January 2025)*

There is some resistance to ciprofloxacin (as a second line agent) by *Pseudomonas aeruginosa* (urinary and non-urinary sites), ESBL-positive *E.coli,* and ESBL-positive *Klebsiella.*

**Comment:** Although not included in this report, the susceptibility results vary between regions, as expected. In the Auckland and Northland community antibiogram, ciprofloxacin was 86% susceptible to *Klebsiella* species where in the West Coast susceptibility ranged from 96-100%. This is important for antimicrobial stewardship and for informing guidelines.

Given the increasing resistance to fluoroquinolones, a mention in the data sheets relating to sensitivity testing seems appropriate, such as: 'due to increasing resistance, consider sensitivity testing prior to use'.

### 2.1.6 New Zealand antibiotic prescribing guidelines and information

*2.1.6.1 Bpac*

Primary Care Antibiotic Guide [11]

The bpac primary care antibiotic guide is a resource for prescribers to assist with the selection of an appropriate antibiotic for patients with infections commonly seen in general practice. It covers a range of infections, of the respiratory, ear, nose and throat, eyes, dental, central nervous system, skin, gastrointestinal and genitourinary systems.

Ciprofloxacin is recommended for:

- Acute exacerbation of bronchiectasis (if P. *aeruginosa* is present)
- Alternative treatment for severe or prolonged campylobacteriosis or high-risk people
- First choice treatment for severe salmonellosis or in high-risk people
- Alternative treatment for yersiniosis severe symptoms or in immunocompromised people
    - Alternative treatment for suspected epididymo-orchitis
    - Alternative treatment for confirmed or suspected gonorrhoea (after discussion with a sexual health physician and/or pathogen is susceptible, and an alternative is required)
- Alternative treatment for acute or chronic bacterial prostatitis
- Alternative treatment of mild pyelonephritis in adults if *Pseudomonas* is suspected/confirmed or the organism is resistant to other alternatives

Moxifloxacin is recommended after initial doxycycline treatment for confirmed M. *genitalium* infection following discussion of a sexual health physician or clinical microbiologist. Norfloxacin is not recommended in this guide.

Limiting the use of quinolone antibiotics [9]

This article highlights that resistance to quinolone antibiotics is increasing, and use of these antibiotics should be limited to serious, life-threatening, or difficult-to-treat infections when other antibiotics cannot be used due to allergy, intolerance, or resistance.

Prescribers are reminded about rare and serious adverse reactions and cautions when prescribing in older people, patients with epilepsy or CNS disorders, and risk factors for adverse reactions.

*2.1.6.2 New Zealand Formulary (NZF)*

The NZF product monograph for quinolones states that quinolones should only be prescribed for serious and/or difficult-to-treat infections for which other antibiotics are considered inappropriate [12]. The monograph links to the bpac article mentioned above and the Prescriber Update article on persisting serious adverse reactions to fluoroquinolones. In addition, there is a blue box warning with information (symptoms, risk factors) on the following ADRs:

- Tendinopathy
- Aortic aneurysm/dissection
- Heart valve regurgitation
- Seizures
- Psychiatric changes
- Peripheral neuropathy

**Comment:** bpac and NZF provide guidance on the indications for use and general considerations when prescribing fluoroquinolones. The bpac article was published in 2021 and although it mentions serious reactions such as tendonitis/tendon rupture, it does not mention that these reactions can be persisting.

Secondary care antibiotic prescribing guidelines have not been included in this section. As discussed above, prescribing of fluoroquinolones in hospital is restricted and requires specialist input.

Antibiotic Conservation Aotearoa is a group of clinicians and researchers working collaboratively across New Zealand to develop a national prescribing standard for antimicrobial use in New Zealand. The national guidelines should be launched this year (2025). It will be interesting to see what the recommendations for fluoroquinolones are.

## 2.2 Regulatory actions and publications

Actions taken by regulatory agencies relating to fluoroquinolones were discussed in the 2017 and 2019 MARC reports referenced at the beginning of this report. At the time, EMA was reviewing the risk of persisting serious side effects mainly affecting muscles, joints and the nervous system associated with fluoroquinolone use. The FDA had updated their boxed warnings about these reactions as well as a statement to reserve fluoroquinolones for use in patients who have no alternative treatment options for the following indications:

- Acute exacerbation of chronic bronchitis
- Acute uncomplicated cystitis
- Acute bacterial sinusitis

The data sheets already included some information on the potential risk of musculoskeletal and nervous system adverse reactions, but the MARC recommended that the data sheets be updated to include information that these reactions could be disabling and persistent. At the time, the MARC did not consider the indications for fluoroquinolones needed restriction.

In 2019 MARC recommended aortic aneurysm/dissection be added to the data sheets of fluoroquinolone antibiotics.

This section provides a summary of recent actions relating to fluoroquinolone antibiotics taken by international regulatory authorities.

**Comments:** Medsafe have published several *Prescriber Update* articles about fluoroquinolones, the most recent articles were Drug-induced tendinopathy (September 2024-note this article includes other medicines) and Reports of persisting serious adverse reactions to fluoroquinolones (September 2023).

As a result of the two previous MARC papers, changes to the data sheet were requested. During this time the funded brand of ciprofloxacin was Cipflox, and the sponsor agreed to the changes requested by Medsafe. Cipflox is no longer marketed, and the data sheet is not publicly available. A copy of this data sheet is attached as Annex 1 for reference.

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### 2.2.1 Medicines and Healthcare products Regulatory Agency

In January 2024 the MHRA published a drug safety update to inform healthcare professionals that systemic fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate [1]. Updates to the UK SPC's to include the following text are required in the therapeutic indications (section 4.1) and undesirable effects (section 4.8) of systemic fluoroquinolone antibiotics:

*Section 4.1: Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:*

- *There is resistance to other first-line antibiotics recommended for the infection;*
- *Other first-line antibiotics are contraindicated in an individual patient;*
- *Other first-line antibiotics have caused side effects requiring treatment to be stopped;*
- *Treatment with other first-line antibiotics has failed*

*Section 4.8: Cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, fatigue, psychiatric symptoms, memory impairment, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the rare frequency category).*

These recommendations add to the restrictions from 2019 where the MHRA recommended that fluoroquinolones should not be prescribed for non-severe or self-limiting infections, and non-bacterial conditions. The reasoning was that the benefit of therapy may not outweigh the risk of severe, prolonged, disabling and potentially irreversible reactions in these indications.

The description of disabling and potentially long-lasting or irreversible side effects in the UK SPC's have also been updated to include psychiatric reactions including sleep disorders, anxiety, panic attacks, confusion, or depression. The incidence rate if these reactions have been updated to a minimum frequency of between 1 and 10 per 10,000 patients.

**Comment:** To date, these are the strongest restrictions on fluoroquinolones taken by a regulatory agency and contrary to other regulatory action, the restricted use covers all indications. It will be interesting to know if/how the MHRA will enforce and measure the outcome of these restrictions.

The updated communication was triggered by the EMA publication (discussed in Section 2.2.2) which showed that fluoroquinolones continue to be prescribed for uncomplicated bacterial infections.

### 2.2.2 European Medicines Agency

In June 2023 the EMA published a direct healthcare professional communication (DHPC) reminding healthcare professionals that systemic and inhaled fluoroquinolones should **not** be prescribed for:

- Patients with previous serious adverse reactions with a quinolone or fluoroquinolone antibiotic;
- Non-severe or self-limiting infections (such as pharyngitis, tonsillitis, and acute bronchitis);
  - Mild to moderate infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease, acute bacterial rhinosinusitis and acute otitis media) unless other antibiotics that are commonly recommended for these infections are considered inappropriate;
- Non-bacterial infections eg non-bacterial (chronic) prostatitis;
- Preventing travellers' diarrhoea or recurrent lower urinary tract infections

These restrictions had been implemented following the EMA review in 2018 mentioned in section 2.2 above.

The DHPC includes information from an EMA-funded study evaluating the impact of the EU label changes for fluoroquinolone medicines. This study (discussed in section 2.2.2.1 below) suggested that fluoroquinolones are still prescribed outside the authorised indications. Healthcare professionals are reminded to advise patients on

the risk of serious adverse reactions, the potential of long-lasting and serious nature of these effects, and to immediately seek a physician at the first signs of these adverse reactions prior to continuing treatment.

*2.2.2.1 Ly et al. 2023. Impact of European Union Label Changes for Fluoroquinolone-containing medicinal products for systemic and inhalation use: post-referral prescribing trends [13]*

Purpose: To examine the impact of EMA regulatory interventions implemented throughout 2018-2019 on fluoroquinolone prescribing rates.

Methods: A retrospective population-based cohort study was conducted using electronic healthcare records from six countries (Belgium, France, Germany, Netherlands, Spain, United Kingdom) between 2016 to 2021. The monthly incident rates of overall and individual fluoroquinolone were reviewed with flexible modelling via segmented regression to detect time points of trend changes and monthly percentage change. The incidence of use was defined as a recorded prescription of fluoroquinolone in patients without use in the previous 30 days.

Subpopulations of interest were investigated and included different age groups, sex, fluoroquinolone type, indication for use, on and off label use, country, and risk groups of interest (at risk of tendinitis/tendon rupture, at risk aortic dissection and aneurism, recent or concomitant corticosteroid exposure).

Results: The incidence of fluoroquinolone prescriptions across countries ranged from 0.7/1,000 persons per month (UK) to 8.0/1,000 persons per month (Spain), and in all countries prescriptions were highest in patients aged >75 years. When the indications for use were reported, respiratory tract infections, uncomplicated urinary tract infections, and ear infections were the most frequent indications.

Changes in prescribing were observed over time across countries, however these were inconsistent and did not seem temporality related to the EMA interventions. Other indicators of changes in prescribing behaviour such as early discontinuation or prescriptions of alternative antibiotics were unaffected by regulatory interventions.

Conclusion: The regulatory actions on reducing fluoroquinolone use associated with the 2018 referral did not have a significant impact on fluoroquinolone prescribing in primary care.

**Comment:** Regulatory action taken by the EMA did not have a significant impact on the prescribing rates of fluoroquinolones in five European countries and the United Kingdom. These findings are similar to a US study which did not identify a statistically significant reduction in the rate of fluoroquinolone prescribing following the implementation of black box warnings.

It was noted that the indications for fluoroquinolone prescribing could not be classified, and unknown indications ranged between 31-94% across different countries. Therefore, the extent to which fluoroquinolone prescribing had been reduced for certain indications no longer approved by the regulatory agency (eg in acute sinusitis, uncomplicated UTIs and acute bronchitis) is unclear.

It is possible that the timeframe of the study was too short to allow dissemination of regulatory changes to impact clinical practice. The study did not have a lag time period, and previous reviews on regulatory risk communications assume a 12-month lag time to evaluate the effects of widespread interventions.

Prior to the implementation of regulatory interventions, the rates of fluoroquinolone prescribing were already decreasing in several countries (Belgium, UK, Spain). These decreases may be attributed to changes in funding and antimicrobial stewardship/clinical guidance. Detection of any effects of regulatory interventions may be obscured by these prior changes.

Part of the study period covered the COVID-19 pandemic which may have influenced the reduction in fluoroquinolone antibiotic prescribing rates.

### 2.2.3 Health Canada

In January 2017, Health Canada issued a risk communication to restrict the use of fluoroquinolone antibiotics due to potentially persistent and disabling side effects. In December 2024 Canda's Drug Agency published the results of a drug utilisation study reviewing the use of fluoroquinolones. A summary of the report is provided below.

*2.2.3.1 Ernst et al. 2024. Use of Oral Fluoroquinolones in Canada: a drug utilisation study update [14].*

Purpose: The study objectives is to describe fluoroquinolone utilisation trends from 2008 to 2022 and assess the impact of regulatory risk minimisation measures introduced in 2017. This report will inform Health Canada on the need for further regulatory actions.

Methods: Multicentre retrospective cohort study using patient electronic healthcare records from six provincial databases across Canada (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan). The study population included individuals with a dispensing of an oral fluroquinolone in the outpatient setting between 2008 and 2022. Separate cohorts were created to identify use of fluoroquinolone for specific indications (acute sinusitis, COPD, uncomplicated UTI's).

Authors used an interrupted time-series analyses to assess the impact of the regulatory actions by estimating the change in the rate of fluoroquinolone dispensings. Use was stratified by fluoroquinolone type, age group, and sex.

**Results: Overall, utilisation of the 4 fluoroquinolones decreased by approximately 50% across provinces, both sexes, and age groups from 2008 to 2022. Fluoroquinolone use declined from approximately 107 to 45.0 dispensations per 1,000 population (Figure 1). Ciprofloxacin remains the most commonly dispensed fluoroquinolone in Canada (**

Figure 2).

Fluoroquinolones were not commonly prescribed for acute bacterial sinusitis and acute exacerbations of COPD, dispensing for these indications declined over the study period. In all provinces, fluoroquinolones (predominantly ciprofloxacin) were frequently dispensed for UTIs although use declined gradually between 2013 and 2022.

**Figure 1: Overall crude dispensation rates (per 1,000 population) for fluoroquinolones of interest by calendar year.**

**Figure 2: Overall crude dispensing rates (per 1,000 population) for each molecule by calendar year.**

Throughout the study period there was a decline in the dispensing rates for fluoroquinolones, even before risk minimisation measures were introduced in 2017. The estimated slope for the trend line from 2008 to 2022 is -0.47 indicating an average reduction of 4.7% (Figure 3).

**Figure 3: Unweighted average monthly dispensing rates for fluoroquinolones with linear trend line**

**The pooled relative rate reduction of fluoroquinolone dispensing after the introduction of risk minimisation measures was estimated to be 0.5 (95%CI 0.43 to 0.59) indicating an estimated 50% reduction in the average age- and sex- adjusted rate from January 2017 to February 2020 (segment 2) relative to the January 2008 to December 2016 reference period (segment 1) (**

Figure 4). These results were similar when data was re-analysed using a 6-month wash out period (segment 3).

**Figure 4: Relative rate of all dispensations of a fluoroquinolone by study segment**

After implementation of risk minimisation measures, the pooled relative rate reduction (adjusted for age and sex) for fluoroquinolones when prescribed for acute bacterial sinusitis was 0.41 (95%CI 0.34 to 0.51) in segment 2 and 0.27 (95%CI 0.18-0.38) in segment 3 (Figure 5).

**Figure 5: Relative rate of fluoroquinolone dispensations by study segment for acute bacterial sinusitis indication**

**After implementation of risk minimisation measures, the pooled relative rate reduction (adjusted for age and sex) for fluoroquinolones when prescribed for acute exacerbations of COPD in patients aged ≥66-years was 0.51 (95%CI 0.37 to 0.69) in segment 2 and 0.23 (95%CI 0.15 to 0.5) in segment 3 (**

Figure 6).

**Figure 6: Relative rate of fluoroquinolone dispensing by study segment for acute exacerbations of COPD indication among people aged ≥66-years**

After implementation of risk minimisation measures, the pooled relative rate reduction for fluoroquinolones when prescribed for uncomplicated UTIs in females was 0.32 (95%CI 0.25 to 0.41) in segment 2 and 0.24 (95%CI 0.17 to 0.35) in segment 3 (Figure 7).

**Figure 7: Relative rate of fluoroquinolone dispensing by study segment for uncomplicated UTI indication among females**

Conclusion: Between 2008 to 2022 there was a decline in the use of oral fluoroquinolones of interest in the outpatient setting. Overall rates of dispensing decreased by approximately 50% across provinces, sexes, and age groups. Rates were declining even before risk minimisation measures were introduced.

The 2017 regulatory actions were followed by reductions in the rate of fluoroquinolone dispensations overall and the percentages of antibiotic dispensations that were fluoroquinolones for the three selected indications: uncomplicated UTI (females), acute exacerbation of COPD (patients aged ≥ 66 years), and acute bacterial sinusitis. These findings could suggest that Health Canada regulatory actions affected the prescribing of oral fluoroquinolones.

**Comment:** Authors of this drug utilisation study found that the dispensing of fluoroquinolones in outpatient settings in Canada reduced over the study period 2008-2022. The most common indications for fluoroquinolones were for genitourinary tract or respiratory infections and the most common fluoroquinolone prescribed was ciprofloxacin.

This decrease was seen across three indications of interest. However, it was noted that the indication for use was not always reported (missing indication ranged between 5-20% across provinces). Differences in coding across the databases may also impact the results.

Authors did not factor in influences on prescribing rates eg changes to local prescribing practice/guidelines, resistance rates, stewardship programs, prescribing criteria, funding criteria which could influence the results. In addition, the COVID-19 pandemic may have impacted community level antibiotic use (especially for respiratory antibiotics).

The 2017 Health Canada regulatory actions were followed by reductions in the rate of fluoroquinolone dispensations however the rates of dispensing were already decreasing prior to 2017. Unmeasured factors, including health care system and patient characteristics, may also have had an impact on fluoroquinolone prescribing.

### 2.2.4 Therapeutic Goods Administration

The TGA have requested a boxed warning class update to the Australian Product Information (PI) for ciprofloxacin, norfloxacin and moxifloxacin products. The boxed warning is located at the top of the PI and repeated in section 4.4 the proposed text is as follows:

***Serious disabling and potentially irreversible adverse reactions.***

*Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions involving different body systems that have occurred together in the same patient. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. These include but are not limited to serious adverse reactions involving the nervous system (see section 4.4 Effects on the CNS), musculoskeletal system (see section 4.4 Tendonitis and tendon rupture) and psychiatric effects (see section 4.4 Psychiatric reactions).*

**Comment:** Medsafe have adopted the EMA's guidance for producing data sheets. Boxed warnings are not required however, companies can include a boxed warning if they consider it helpful. However, studies from the US suggest there is limited benefit of a boxed warning on changes to prescribing rates.

## 2.3 Data sheets

This section provides a summary of the key differences in indications and known safety concerns for fluoroquinolones in New Zealand compared with international product information. When available the New Zealand data sheets were compared against the equivalent Australian PI, UK SPC, and European (Dutch or Irish) SmPC.

### 2.3.1 Review of indications

The New Zealand indications for fluoroquinolones are listed in 2.1.1.

Ciprofloxacin

The Australian PI, UK SPC, and Ireland SmPC product information for ciprofloxacin list the following indications: urinary tract infections, gonorrhoeal urethritis and cervicitis, gastroenteritis, bronchial infections, skin and skin structure infections, bone and joint infections, bacterial prostatitis, pelvic infections [15-17].

The Irish SmPC contains the following wording for acute exacerbations of COPD and uncomplicated cystitis (Figure 8).

**Figure 8: Profloxcin indications (Irish SmPC) [17]:**

Lower respiratory tract infections due to Gram-negative bacteria

- exacerbations of chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease, Profloxin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- pneumonia

Uncomplicated acute cystitis
In Uncomplicated acute cystitis, Profloxin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Moxifloxacin

The Australian Avelox PI, and Dutch Erelan SmPC indications are consistent with the New Zealand indications. The UK Avelox SPC contains information on restricted indications as per section 2.2.1 [7, 18-20].

The Dutch SmPC contains the following wording for acute bacterial sinusitis and acute exacerbations of COPD (Figure 9). In addition, moxifloxacin is not recommended in use as monotherapy in mild to moderate pelvic inflammatory disease to due increasing resistance and should not be used to initiate therapy for any type of skin and skin structure infection or in severe community acquired pneumonia.

**Figure 9: Erelan indications (Dutch SmPC) [20]**

Acute bacterial sinusitis (adequately diagnosed).
In acute bacterial sinusitis Erelan should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
Acute exacerbation of chronic obstructive pulmonary disease including bronchitis. In acute exacerbation of chronic obstructive pulmonary disease Erelan should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Norfloxacin

The New Zealand and Australian Norfloxacin indications cover complicated and uncomplicated urinary tract infections, and bacterial gastroenteritis infections [21]. The New Zealand data sheet also covers gonococcal infections. It does not state any of the restricted indications mentioned above.

**Comment:** Overall, the New Zealand fluoroquinolone indications for use are generally consistent with international information but lack some specific text regarding potential restricted use. Note that the indication for ciprofloxacin in NZ starts with 'Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens'.

As stated in 2.2.1 the UK SPC's state that fluoroquinolone should only be used when other first-line treatments are not suitable regardless of the indication.

For ciprofloxacin the Irish SmPC states that for exacerbations of COPD and uncomplicated acute cystitis, ciprofloxacin should be used when it is inappropriate to use other antibacterial agents. A similar warning can be found in the moxifloxacin Dutch SmPC for the indication's acute bacterial sinusitis, acute exacerbations of COPD (including bronchitis). Similar information is included in product information from Canada, Switzerland, and the US.

The EMA 2018 and MHRA 2019 recommendations state that fluoroquinolones should not be used for mild to moderate infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease, acute bacterial rhinosinusitis, and acute otitis media) unless other antibiotics that are commonly recommended for these infections are considered inappropriate. Similar recommendations have been made by Swissmedic and FDA.

The MARC could consider whether restrictions for use similar to the UK and/or Irish restrictions are required in the New Zealand data sheets or any other changes to the indications

### 2.3.2 Review of safety concerns

Section 2.1.4 lists the known safety concerns of fluoroquinolone antibiotics that could be listed in section 4.4 of the data sheet. **Error! Reference source not found.** highlights whether these safety concerns are currently listed in section 4.4 (or 4.8) of the data sheets for approved products available in New Zealand. Note that even if listed, the information may not be as comprehensive as may be desired, see Tables 5-17 below.

Please refer to **Annex 2** which contains a comparison of the wording for each safety concern by product and country/region.

**Table 4: Review of special warnings/precautions listed in the New Zealand data sheets for fluoroquinolone products [3-6, 19]**

| Special warning/ precaution for use | Product | | | | |
|---|---|---|---|---|---|
| | Ipca-Ciprofloxacin | Aspen Ciprofloxacin | Avelox | Moxifloxacin Kabi | Arrow-Norfloxacin |

| | | | | | |
|---|---|---|---|---|---|
| Prolonged, disabling, and potentially irreversible serious adverse drug reactions | | | | | |
| QTc prolongation | | | | | |
| Hypersensitivity and allergic reactions | | | | | |
| Hepatic disorders | | | | | |
| Severe cutaneous adverse reactions (SJS,TEN, DRESS) | * | ** | * | * | * |
| Seizures | | | | | |
| Peripheral neuropathy | | | | | |
| Psychiatric reactions | | | | | |
| Antibiotic associated diarrhoea and colitis | | | | | |
| Myasthenia gravis | | | | | |
| Tendinitis and tendon rupture | | | | | |
| Aortic aneurysm and dissection | | | | | |
| Vision disorders | | | | | |
| Hypo-hyper glycaemia | | | | | |
| Photosensitivity reactions | | | | | |
| Haemolytic reactions (G6PD deficiency) | | | | | |

**Key:**

- **Green:** listed in section 4.4 and 4.8
- **Yellow:** not listed in section 4.4 but listed in 4.8
- **Red:** not listed
- * SJS and TEN
- ** SJS, TEN, and DRESS

*2.3.2.1 Ciprofloxacin*

Several inconsistencies have been identified in the Ipca-Ciprofloxacin data sheet compared with international equivalents. The key differences in the information are summarised below in Tables 5-17:

**Table 5: Ciprofloxacin wording on general warnings and prolonged, disabling, and potentially irreversible serious adverse reactions.**

| Product | Safety concern: General warnings and information on prolonged, disabling, and potentially irreversible serious adverse drug reactions. |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Fluoroquinolones have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon |

| | |
|---|---|
| | rupture, peripheral neuropathy, and neuropsychiatric effects. See Nervous System and Musculoskeletal system section 4.4 Special warnings and precautions for use<br>**Comment: There is limited information on this safety concern, prolonged, disabling and potentially persistent serious ADRs could be listed under a subheading. Consider updating the warning to include information on lack of pharmacological treatment, discontinuation of therapy if symptoms occur.** |
| Aspen Ciprofloxacin (NZ) | Identified precautions<br>Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and central nervous system effects.<br>**Comment: Similarly to the Ipca-Ciprofloxacin data sheet, this information should be updated.** |
| Ciprofloxacin Sandoz (AU) | Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. These include, but are not limited to, serious adverse reactions involving the nervous system (see CNS effects, below), musculoskeletal system (see Effects on tendons, below) and psychiatric effects (see Psychiatric reactions, below)<br>**Comment: There is no subheading for this safety concern, note this is also a boxed label at the top of the PI** |
| Ciprofloxacin (UK) | The use of ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).<br>Prolonged, disabling and potentially irreversible serious adverse drug reactions<br>Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.<br>**Comment: The UK wording contains additional information on a lack of treatment options, and warnings for patients to seek care if they develop symptoms.** |
| Profloxcin (Ireland) | The use of Ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).<br>Prolonged, disabling and potentially irreversible serious adverse drug reactions<br>Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, |

| | |
|---|---|
| | sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.<br>**Comment: The UK and Ireland wording is very similar. The Ireland wording contains a frequency of very rare.** |

**Table 6: Ciprofloxacin wording on prolongation of QTc interval**

| Product | Safety concern: Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions: |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Cardiac disorders<br>Ciprofloxacin is associated with cases of QT prolongation (see 4.8 Undesirable effects). In general, elderly patients may be more susceptible to medicine associated effects on the QT interval. Precaution should be taken when using ciprofloxacin with concomitant medicines that can result in prolongation with the QT interval (e.g., class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia)<br>**Comment: This is less informative compared to international prescribing information- consider aligning the wording with the UK/EU SPC.** |
| Aspen Ciprofloxacin (NZ) | Cardiac disorders:<br>Ciprofloxacin is associated with cases of QT prolongation (see section 4.8 Undesirable effects). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT prolongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant medicines that can result in prolongation with the QT interval (e.g. Class IA or III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)) or in patients with risk factors for QT prolongation or torsade de pointes (e.g. congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia)<br>**Comment: Aligned with international information.** |
| Ciprofloxacin Sandoz (AU) | Aligned with the Aspen-Ciprofloxacin data sheet |
| Ciprofloxacin (UK) | Cardiac disorders<br>Caution should be taken when using fluoroquinolones, including Ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:<br>• congenital long QT syndrome<br>• concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)<br>• uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)<br>• cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)<br>Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including Ciprofloxacin, in these populations.<br>**Comment: The information is consistent with Aspen-Ciprofloxacin.** |

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| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 7: Ciprofloxacin wording on hepatic disorders**

| Product | Safety concern: Hepatic disorders |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Gastrointestinal system (4.4)<br>There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.<br>Adverse reaction (4.8)<br>Hepatobiliary disorders<br>Hepatic impairment, Jaundice, Hepatitis (non-infective), liver necrosis (very rarely progressing to life-threatening hepatic failure)<br>**Comment: Does not list that hepatitis potentially leading to liver failure can occur in 4.4, although does mention this in section 4.8. The wording in 4.4 could be strengthened and listed under a different subheading.** |
| Aspen Ciprofloxacin (NZ) | Effects on the liver<br>There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.<br>Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued. There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin<br>**Comment: Mentions changes in LFTs and information on hepatic necrosis which is consistent with other fluoroquinolones.** |
| Ciprofloxacin Sandoz (AU) | Aligns with Aspen-Ciprofloxacin. |
| Ciprofloxacin (UK) | Hepatobiliary system<br>Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus or tender abdomen), treatment should be discontinued.<br>**Comments: Aligns with the EU SmPC.** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 8: Ciprofloxacin wording on severe cutaneous adverse reactions**

| Product | Safety concern: Severe cutaneous adverse reactions |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Adverse reactions post-marketing (4.8)<br>Skin and subcutaneous tissue disorders<br>Erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), Toxic epidermal necrolysis (potentially life-threatening).<br>**Comment: SCARs are not listed in 4.4, SJS, TEN are listed in 4.8.**<br>**DRESS is not listed.** |
| Aspen Ciprofloxacin (NZ) | Hypersensitivity Reactions<br>Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been reported extremely rarely in patients receiving ciprofloxacin along with other drugs. The |

| | |
|---|---|
| | possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity<br>Adverse reactions (4.8)<br>Skin/hypersensitivity<br>erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, hyperpigmentation, erythema nodosum, erythema multiforme exudativum (minor), papules, petechiae, Lyell syndrome, haemorrhagic bullae, serum-sickness like reaction, fixed eruption, drug reaction with eosinophilia and systemic symptoms (DRESS)<br>**Comment: SCARs are not specifically mentioned in 4.4 but the hypersensitivity section lists rash, fever, eosinophilia which may be a symptom of DRESS.**<br>**SJS, TEN and DRESS are listed in 4.8.** |
| Ciprofloxacin Sandoz (AU) | Aligned with the UK and Irish SmPC<br>**Comment: SCARs are not listed in 4.4, SJS, TEN and DRESS are listed in 4.8** |
| Ciprofloxacin (UK) | Adverse reactions (4.8)<br>Skin and subcutaneous tissue disorders<br>Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening), acute generalised exanthematous pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<br>**Comment: SCARs are not listed in 4.4, SJS, TEN and DRESS are listed in 4.8** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 9: Ciprofloxacin wording on seizures**

| Product | Safety concern: Seizures |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Nervous System:<br>In epileptics and in patients who have suffered from previous CNS-disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are at risk because of possible central-nervous side effect<br>Adverse reactions (4.8)<br>Nervous system disorders<br>Seizure<br>**Comment: Section 4.4 talks about patients with CNS disorders but does not mention that fluoroquinolones can trigger seizures/have been reported with therapy. Seizures are only listed in 4.8 but information should be included in 4.4 (consider the wording in the UK ciprofloxacin SPC- or a separate subheading as seen in the moxifloxacin data sheet).** |
| Aspen Ciprofloxacin (NZ) | Central Nervous System (CNS) Disorders<br>As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, dizziness, light headedness, confusion, and very rarely to hallucinations or convulsive seizures. These reactions may occur following the first dose. If these reactions do occur in patients receiving ciprofloxacin, the drug should be discontinued, and appropriate measures instituted. Increased intracranial pressure and toxic psychosis have also been reported in patients receiving quinolones, including ciprofloxacin. |

| | |
|---|---|
| | **Comment: Aligns with the Australian PI and covers a variety of CNS events (not just seizures)** |
| Ciprofloxacin Sandoz (AU) | Aligns with the Aspen Ciprofloxacin data sheet |
| Ciprofloxacin (UK) | Central nervous system<br>Ciprofloxacin like other quinolones is known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur, ciprofloxacin should be discontinued.<br>**Comment: Provides clear information that ciprofloxacin/fluoroquinolones can trigger seizures.** |
| Profloxin (Ireland) | Central Nervous System<br>Quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported.<br>Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8).<br>**Comment: Provides clear information that ciprofloxacin/fluoroquinolones can trigger seizures, also contains information on psychiatric reactions.** |

**Table 10: Ciprofloxacin wording on psychiatric reactions**

| Product | Safety concern: Psychiatric reactions |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Nervous system<br>In some instances the CNS reactions occurred after the first administration of ciprofloxacin. In rare cases depression or psychosis can progress to self-endangering behaviour. In these cases ciprofloxacin has to be discontinued and the doctor should be informed immediately<br>**Comment: Compared to other ciprofloxacin prescribing information (and other fluoroquinolones) there is little information in 4.4 on psychiatric reactions. It's noted that some reactions (agitation, confusion, anxiety, depression, hallucinations and psychotic reactions) are listed in 4.8. Given these reactions can be long lasting and significant for a patient, information on these reactions should be listed in section 4.4.** |
| Aspen Ciprofloxacin (NZ) | Psychiatric reactions:<br>Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving ciprofloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care<br>**Comment: Aligns with AU and consistent with the class warning. Contains more information on psychiatric symptoms compared to the UK and Irish SmPC.** |
| Ciprofloxacin Sandoz (AU) | Aligns with Aspen Ciprofloxacin |
| Ciprofloxacin (UK) | Psychiatric reactions |

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| | Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychoses can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, treatment should be discontinued (see section 4.8).<br>**Comment: Contains the general class warning but less detailed than the AU PI. It's noted that some reactions (agitation, confusion, anxiety, depression, hallucinations, and psychotic reactions) are listed in 4.8 and states that these reactions can be persistent.** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 11: Ciprofloxacin wording on peripheral neuropathy**

| Product | Safety concern: Peripheral neuropathy |
|---|---|
| Ipca-Ciprofloxacin (NZ) | General statement<br>Fluoroquinolones have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects. See Nervous system and Musculoskeletal system section 4.4 Special warnings and precautions for use.<br>**Comment: Compared to other ciprofloxacin prescribing information (and other fluoroquinolones) there is little information in 4.4 on peripheral neuropathy. This information should be included in 4.4** |
| Aspen Ciprofloxacin (NZ) | Peripheral neuropathy<br>Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy such as pain, burning, tingling, numbness, and/or weakness develop in order to prevent the development of an irreversible condition (see section 4.8 Undesirable effects).<br>**Comment: Consistent with the class warning and aligns with the AU PI** |
| Ciprofloxacin Sandoz (AU) | Aligns with the Aspen Ciprofloxacin data sheet. |
| Ciprofloxacin (UK) | Peripheral neuropathy<br>Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition. (see section 4.8).<br>**Comment: Consistent with the class warning.** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 12: Ciprofloxacin wording on antibiotic associated diarrhoea and colitis**

| Product | Safety concern: Antibiotic associated diarrhoea and colitis |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Gastrointestinal System<br>In the event of severe and persistent diarrhoea during or after treatment a doctor must be consulted, since this symptom can hide a serious intestinal disease (life-threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment. In such cases Ciprofloxacin must be discontinued and |

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| | appropriate therapy initiated (e. g. vancomycin, orally, 4 x 250 mg/day). Medicines that inhibit peristalsis are contraindicated.<br>**Comment: Contains less information than other fluoroquinolone products, consider requesting an update to align with the class warning statement.** |
| Aspen Ciprofloxacin (NZ) | Antibiotic-associated Colitis<br>Antibiotic-associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases, appropriate therapy such as oral antibacterial agents effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used<br>**Comment: Consistent with the general class warning** |
| Ciprofloxacin Sandoz (AU) | Antibiotic associated colitis<br>Antibiotic associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea. Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to medicine discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against C. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Medicines, which delay peristalsis such as: opiates and diphenoxylate with atropine, may prolong and/or worsen the condition and should not be used<br>**Comment: Consistent with the general class warning** |
| Ciprofloxacin (UK) | Gastrointestinal system<br>The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases ciprofloxacin should be discontinued immediately and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.<br>**Comment: Aligns with the EU SmPC- however the moxifloxacin SPC and SmPC contain more information.** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 13: Ciprofloxacin wording on myasthenia gravis**

| Product | Safety concern: Myasthenia gravis |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Adverse reactions (4.8)<br>Musculoskeletal, Connective Tissue and Bone Disorders<br>Exacerbation of symptoms of myasthenia gravis |

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| | **Comment: Not listed as a warning under 4.4- consider adding to align with the class of fluoroquinolones.** |
| Aspen Ciprofloxacin (NZ) | Myasthenia gravis<br>Ciprofloxacin might exacerbate symptoms of myasthenia gravis. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted<br>**Comment: This information is acceptable and aligns with the AU PI.** |
| Ciprofloxacin Sandoz (AU) | Aligns with the Aspen Ciprofloxacin NZ data sheet |
| Ciprofloxacin (UK) | Musculoskeletal system<br>Ciprofloxacin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated (see section 4.8).<br>**Comment: Aligns with the class warning** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 14: Ciprofloxacin wording on tendonitis and tendon rupture**

| Product | Safety concern: Tendonitis and tendon rupture |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Musculo-Skeletal System<br>At any sign of tendinitis (e.g. painful swelling, inflammation), a physician should be consulted and the antibiotic treatment be discontinued. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to increased risk of tendon rupture. Tendon rupture (predominantly Achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment.<br>**Comment: A subheading on tendonitis and tendon rupture should be added to the Ipca-Ciprofloxacin data sheet, it should align with international prescribing information and include information that the reaction can occur within 48 hours or several months after discontinuation and may cause prolonged disability as per the AU information.** |
| Aspen Ciprofloxacin (NZ) | Tendon rupture<br>Fluoroquinolones may cause tendonitis or tendon rupture. The risk of tendonitis or tendon rupture is increased in patients: over the age of 60 years; on concomitant systemic steroid therapy; who have received a kidney, heart or lung transplant. Fluoroquinolones should not be used in patients with a history of fluoroquinolone associated tendonopathy. Tendonitis and tendon rupture risk is present during use and for 6 months following use of fluoroquinolone. Prescribers should advise patients that at the first sign of tendon pain, inflammation or tendon rupture, to stop taking the fluoroquinolone, avoid exercise or use of the affected area and immediately contact their doctor<br>**Comment: This statement is less informative compared to the AU, UK, EU information, consider aligning with the wording used in international product information,** |
| Ciprofloxacin Sandoz (AU) | Effects on tendons<br>Tendonitis and other tendon ruptures (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. This may occur even within the first 48 hours of treatment or up to several months after discontinuation of ciprofloxacin. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with |

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| | corticosteroids, in patients with renal impairment and in patients with solid organ transplants. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any signs of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise, a physician should be consulted, and the antibiotic treatment should be discontinued due to the increased risk of tendon rupture.<br>**Comment: Aligns with the general class warning. States that tendonitis and tendon ruptures can result in prolonged disability.** |
| Ciprofloxacin (UK) | Tendinitis and tendon rupture<br>Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation), the treatment with ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.<br>**Comment: Aligns with the EU SmPC and general class warning.** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 15: Ciprofloxacin wording on dysglycaemia**

| Product | Safety concern: Dysglycaemia |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Special warnings and precautions for use<br>May cause tendinitis, hypoglycaemia.<br>**Comment: This data sheet is inconsistent with compared with other ciprofloxacin, moxifloxacin and norfloxacin data sheets. The sponsor should include information on dysglycaemia in section 4.4 of the data sheet.** |
| Aspen Ciprofloxacin (NZ) | Dysglycaemia<br>As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with ciprofloxacin. In ciprofloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8 Undesirable effects).<br>**Comment: Aligns with the class warning.** |
| Ciprofloxacin Sandoz (AU) | Aligns with the Aspen Ciprofloxacin NZ data sheet and Irish SmPC. |
| Ciprofloxacin (UK) | Hypoglycaemia<br>As with other quinolones, hypoglycaemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).<br>Dysglycaemia |

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| | As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.<br>**Comment: Aligns with the class warning but has an extra paragraph on hypoglycaemia.** |
| Profloxin (Ireland) | Identical wording to the Aspen Ciprofloxacin data sheet and AU PI. |

**Table 16: Ciprofloxacin wording on G6PD deficiency**

| Product | Safety concern: G6PD deficiency |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Adverse reaction (4.8)<br>Haemolytic anaemia<br>**Comment: Lists haemolytic anaemia as an ADR in 4.8, but no information on G6PD deficiency- this should be added to the data sheet.** |
| Aspen Ciprofloxacin (NZ) | Adverse reaction (4.8)<br>Haemolytic anaemia<br>**Comment: Lists haemolytic anaemia as an ADR in 4.8, but no information on G6PD deficiency- this should be added to the data sheet.** |
| Ciprofloxacin Sandoz (AU) | Adverse reaction (4.8)<br>Haemolytic anaemia<br>**Comment: Lists haemolytic anaemia as an ADR in 4.8, but no information on G6PD deficiency** |
| Ciprofloxacin (UK) | Glucose-6-phosphate dehydrogenase deficiency<br>Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.<br>**Comment: Aligns with the EU SmPC and other medicines in the fluoroquinolone class.** |
| Profloxin (Ireland) | Identical wording to the UK SPC. |

**Table 17: Ciprofloxacin wording on vision disorders**

| Product | Safety concern: Vision disorders |
|---|---|
| Ipca-Ciprofloxacin (NZ) | Adverse reactions (4.8)<br>Eye disorders<br>Visual disturbances, visual colour distortions<br>**Comment: There is no information on vision disorders in section 4.4, the sponsor could include a warning to align with the class warning.** |
| Aspen Ciprofloxacin (NZ) | Vision disorders<br>If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see section 4.8 Undesirable effects).<br>**Comment: This information aligns with the class warning.** |
| Ciprofloxacin Sandoz (AU) | Identical wording to the Aspen Ciprofloxacin NZ data sheet, UK SPC and Ireland SmPC. |
| Ciprofloxacin (UK) | Identical wording to the Aspen Ciprofloxacin NZ data sheet, AU PI, and Ireland SmPC. |

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| Profloxin (Ireland) | Identical wording to the Aspen Ciprofloxacin NZ data sheet, AU PI, and UK SPC |

**Comment:** As pictured on Table 4-17 there are inconsistencies in the information on known safety concerns especially in the Ipca-Ciprofloxacin data sheet. Warnings about aortic aneurysm and dissection are completely missing,

The MARC could advise whether section 4.4 requires updating. For example this section could be updated in regard to prolonged, disabling and potentially persisting serious adverse reactions, QTc prolongation, hepatic disorders, seizures, psychiatric reactions, peripheral neuropathy, antibiotic associated diarrhoea and colitis, aortic aneurysm and dissection, tendonitis and tendon rupture, myasthenia gravis, dysglycaemia, G6PD deficiency and vision disorders.

The MARC should consider whether DRESS should be added as an ADR in section 4.8 or included as a warning in 4.4.

Concerns have been raised specifically around the wording of prolonged, disabling, and potentially persistent serious adverse drug reactions. Internationally the product information uses the word 'irreversible' instead of 'persistent', we request the MARC to advise if the terminology should be changed.

*2.3.2.2 Moxifloxacin*

Compared to ciprofloxacin the product information for moxifloxacin is generally more consistent. The key differences in the information are summarised below in Tables 18-26:

**Table 18: Moxifloxacin wording on general warnings and information on prolonged, disabling and potentially irreversible serious adverse reactions**

| Product | Safety concern: Prolonged, disabling, and potentially irreversible serious adverse drug reactions. |
|---|---|
| Avelox (NZ) | Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system and musculoskeletal system.<br>**Comment: Consider aligning to the UK wording which contains more information about these serious adverse reactions. This information should be included under a subheading and link to various sections in 4.4.** |
| Avelox (AU) | Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially irreversible adverse reactions involving different body systems that have occurred together in the same patient. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. These include, but are not limited to, serious adverse reactions involving the nervous system (see Section 4.4 Seizures and Peripheral neuropathy, below), musculoskeletal system (see Section 4.4 Tendonitis and tendon rupture, below) and psychiatric effects (see Section 4.4 Psychiatric reactions).<br>**Comment: This is stated in section 4.4 and also included as a boxed warning at the top of the PI** |
| Avelox (UK) | The use of moxifloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3). |

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| | The benefit of moxifloxacin treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section.<br>Prolonged, disabling and potentially irreversible serious adverse drug reactions<br>Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Moxifloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.<br>**Comment: The UK wording contains additional information on a lack of treatment options, and warnings for patients to seek care if they develop symptoms.** |
| Ereland (Netherlands) | The use of moxifloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).<br>The benefit of moxifloxacin treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section.<br>Prolonged, disabling and potentially irreversible serious adverse drug reactions<br>Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Moxifloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.<br>**Comment: The UK and Dutch wording is very similar. The Dutch wording contains a frequency of very rare.- This wording is the same in the Irish SmPC for ciprofloxacin.** |

**Table 19: Moxifloxacin wording on hypersensitivity/allergic reactions**

| Product | Safety concern: Hypersensitivity/allergic reactions |
|---|---|
| Avelox (NZ) | Hypersensitivity<br>In some instances, the hypersensitivity and allergic reactions occurred after the first administration and the doctor should be informed immediately.<br>Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Avelox must be discontinued, medical treatment (e.g. treatment for shock) is required.<br>Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Avelox. Patients should be advised to contact |

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| | their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.<br>**Comment: Information on anaphylactic reactions (including shock) are consistent compared to the international prescribing information. The NZ data sheet lists SJS and TEN under this section.** |
| Avelox (AU) | Hypersensitivity Reactions<br>Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued, and appropriate therapy commenced in these cases.<br>Anaphylactic reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.<br>**Comment: The Australian, UK, and European information is aligned.** |
| Avelox (MHRA) | Aligned with AU PI and EU SmPC |
| Ereland (Netherlands) | Aligned with AU PI and UK SPC |

**Table 20: Moxifloxacin wording on hepatic disorders**

| Product | Safety concern: Hepatic disorders |
|---|---|
| Avelox (NZ) | Hepatobiliary system<br>Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with Avelox (see Section 4.8 Undesirable effects). Patients should be advised to contact their doctor immediately prior to continuing treatment if symptoms related to liver failure occur.<br>**Comment: Generally aligns with the AU, UK, and EU information but does not list the symptoms of hepatitis nor does it list that LFTs need to be monitored. Given the data sheet is aimed at healthcare professionals this is acceptable.** |
| Avelox (AU) | Patients with severe hepatic impairment<br>As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing adverse event reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.<br>**Comment: Similar to the UK and EU SmPC, contains a warning that limited clinical data is available for patients with severe hepatic impairment.** |
| Avelox (MHRA) | Severe liver disorders<br>Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur. |

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| | **Comment: Aligns with the EU SmPC** |
| Ereland (Netherlands) | Aligns with UK SPC. |

**Table 21: Moxifloxacin wording on severe cutaneous adverse reactions**

| Product | Safety concern: Severe cutaneous adverse reactions |
|---|---|
| Avelox (NZ) | Adverse reactions (4.8)<br>Skin and subcutaneous tissue disorders<br>Bullous skin reactions like Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)<br>**Comment: SCARs are not listed as a separate subheading in 4.4, SJS and TEN are listed in 4.8, DRESS is not listed.** |
| Avelox (AU) | Skin Reactions<br>Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing adverse event reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.<br>**Comment: SJS and TEN are listed in 4.4 and 4.8. DRESS is not listed.** |
| Avelox (MHRA) | Adverse reactions (4.8)<br>Skin and subcutaneous tissue disorders<br>Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening), acute generalised exanthematous pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<br>**Comment: SCARs are not listed in 4.4, SJS, TEN and DRESS are listed in 4.8** |
| Ereland (Netherlands) | Severe cutaneous adverse reactions<br>Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) Acute Generalised Exanthematous Pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which could be life-threatening or fatal, have been reported with moxifloxacin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, moxifloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN, AGEP or DRESS with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.<br>**Comment: Only the EU SmPC lists SCARs (including DRESS) as a warning in 4.4 and ADR in 4.8** |

**Table 22: Moxifloxacin wording on seizures**

| Product | Safety concern: Seizures |
|---|---|
| Avelox (NZ) | Seizures<br>Seizures may occur with fluoroquinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, |

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| | altered brain structure or stroke), which may predispose to seizures or lower the seizure threshold.<br>**Comment: Consistent with the UK/EU SmPC but does not state that the medicine should be discontinued, and the appropriate measures initiated. Given the data sheet is aimed at healthcare professionals this is acceptable.** |
| Avelox (AU) | Aligns with the NZ data sheet |
| Avelox (MHRA) | Patients predisposed to seizures<br>Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold. In case of seizures, treatment with moxifloxacin should be discontinued and appropriate measures instituted.<br>**Comment: Aligns with the EU SmPC.** |
| Ereland (Netherlands) | Aligns with the UK SPC |

**Table 23: Moxifloxacin wording on psychiatric reactions**

| Product | Safety concern: Psychiatric reactions |
|---|---|
| Avelox (NZ) | Psychiatric reactions<br>Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases, depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behavior such as suicide attempts (see Section 4.8 Undesirable effects). In the event that the patient develops these reactions, Avelox should be discontinued, and appropriate measures instituted. Caution is recommended if Avelox is to be used in psychotic patients or in patients with a history of psychiatric disease<br>**Comment: Aligns with international prescribing information but could use wording similar to Australia which lists more symptoms.** |
| Avelox (AU) | Psychiatric reactions<br>Fluoroquinolones, including moxifloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving moxifloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care<br>**Comment: Contains slightly more information on symptoms of psychiatric reactions.** |
| Avelox (MHRA) | Psychiatric reactions<br>Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts (see section 4.8). In the event that the patient develops these reactions, moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.<br>**Comment: Aligns with the EU SmPC** |
| Ereland (Netherlands) | Aligns with the UK SPC |

**Table 24: Moxifloxacin wording on antibiotic associated diarrhoea and colitis**

| Product | Safety concern: Antibiotic associated diarrhoea and colitis |
|---|---|
| Avelox (NZ) | Gastrointestinal system<br>Antibiotic associated colitis has been reported with the use of broad-spectrum antibiotics including Avelox and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of Avelox. If antibiotic associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation<br>**Comment: Aligns with the class warning- however has slightly less information that the UK and EU SPC/SmPC.** |
| Avelox (AU) | Antibiotic-associated Colitis<br>Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea<br>**Comment: Aligns with the class warning, but doesn't specify the term antibiotic-associated diarrhoea** |
| Avelox (MHRA) | Antibiotic-associated diarrhoea incl. colitis<br>Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.<br>**Comment: Aligns with the EU SmPC** |
| Ereland (Netherlands) | Aligns with the UK SPC |

**Table 25: Moxifloxacin wording on G6PD deficiency**

| Product | Safety concern: G6PD deficiency |
|---|---|
| Avelox (NZ) | **Comment: There is no information in the PI about patients with G6PD deficiency and haemolytic reactions. The sponsor should be asked to include a statement in section 4.4.** |
| Avelox (AU) | **Comment: There is no information in the PI about patients with G6PD deficiency and haemolytic reactions** |

| | |
|---|---|
| Avelox (MHRA) | Patients with glucose-6-phosphate dehydrogenase deficiency<br>Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.<br>**Comment: Aligns with the EU SmPC and other medicines in the fluoroquinolone class.** |
| Ereland (Netherlands) | Aligns with the UK SPC |

**Table 26: Moxifloxacin wording on vision disorders**

| Product | Safety concern: Vision disorders |
|---|---|
| Avelox (NZ) | Adverse reactions (4.8)<br>Eye disorders<br>Transient loss of vision (especially in the course of CNS reactions)<br>**Comment: Inconsistent compared to other data sheets- consider adding a warning to 4.4 to align with the class warning** |
| Avelox (AU) | Vision disorders<br>If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8)<br>**Comment: Aligns with UK SPC and EU SmPC** |
| Avelox (MHRA) | Aligns with AU PI, EU SmPC and general class warning |
| Ereland (Netherlands) | Aligns with AU PI, UK SPC and general class warning |

**Comment:** The sponsor should be asked to update section 4.4 with information on prolonged, disabling and potentially persistent serious adverse reactions, vision disorders, G6PD deficiency.

The New Zealand data sheet lists SJS and TEN as warnings under hypersensitivity reactions. The EU SmPC is the only product information that lists SCARs (including DRESS) as a warning in 4.4. It is noted that DRESS is listed as an ADR in the UK and EU SmPC but not in the New Zealand or Australian information. The MARC should consider if DRESS should be included as a warning or an ADR.

*2.3.2.3 Norfloxacin*

The summary of differences between the New Zealand and Australian Product Information for norfloxacin is described below in Tables 27-32:

**Table 27: Norfloxacin wording on general warnings and prolonged, disabling, and potentially irreversible serious adverse drug reactions**

| Product | Safety concern: General warnings and information on prolonged, disabling, and potentially irreversible serious adverse drug reactions. |
|---|---|
| Arrow Norfloxacin (NZ) | Fluoroquinolones have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.<br>**Comment: There is no separate subheading for this safety concern- this information is limited compared to international class labels (eg ciprofloxacin UK SPC). The data sheet should be updated.** |
| Apo-Norfloxacin (AU) | Fluoroquinolones, including APO-NORFLOXACIN, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. These include, but are not limited to, serious adverse reactions involving the nervous |

| | |
|---|---|
| | system (see Nervous system) and musculoskeletal system (see Effect on tendons) and psychiatric effects (see Psychiatric adverse reactions).<br>Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated<br>**Comment: There is no subheading for this safety concern, note this is also a boxed label at the top of the PI. Contains a sentence about reserving use.** |

**Table 28: Norfloxacin wording on severe cutaneous adverse reactions**

| Product | Safety concern: Severe cutaneous adverse reactions |
|---|---|
| Arrow-Norfloxacin (NZ) | Adverse reactions (4.8)<br>Skin and subcutaneous tissue disorders<br>Skin reactions, exfoliative dermatitis, toxic epidermal necrolysis (Lyell´s syndrome), erythema multiforme (Stevens-Johnson syndrome), photosensitivity (see section 4.4 Special warnings and precautions for use"), pruritus, urticaria, angioedema, petechiae, bullous haemorrhagic dermatosis<br>**Comment: SCARs are not listed in 4.4. SJS and TEN are listed in 4.8, DRESS is not listed.** |
| Apo-Norfloxacin (AU) | Post marketing adverse reactions (4.8)<br>Hypersensitivity Reactions:<br>These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).<br>Skin:<br>Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus and leukocytoclastic vasculitis<br>**Comment: SCARs are not listed in 4.4, SJS, TEN and DRESS are listed in 4.8** |

**Table 29: Norfloxacin wording on seizures**

| Product | Safety concern: Seizures |
|---|---|
| Arrow-Norfloxacin (NZ) | Use in patients with epilepsy and other CNS disorders<br>Norfloxacin should only be used if there is an overwhelming clinical need in patients with known epilepsy or disorders which lower the seizure threshold. Convulsions have been reported in rare cases in patients receiving norfloxacin. Norfloxacin may lead to exacerbation and aggravation of the symptoms in patients with known or suspected psychiatric disorders, hallucinations and/or confusion. In case of convulsive seizures, treatment with norfloxacin should be discontinued.<br>**Comment: Consider aligning with the wording in the NZ moxifloxacin data sheet:**<br>*Seizures*<br>*Seizures may occur with fluoroquinolone therapy (name) should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), which may predispose to seizures or lower the seizure threshold.* |
| Apo-Norfloxacin (AU) | Nervous system |

| | |
|---|---|
| | The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.<br>**Comment: N/A** |

**Table 30: Norfloxacin wording on psychiatric reactions**

| Product | Safety concern: Psychiatric reactions |
|---|---|
| Arrow-Norfloxacin (NZ) | Use in patients with epilepsy and other CNS disorders<br>Norfloxacin may lead to exacerbation and aggravation of the symptoms in patients with known or suspected psychiatric disorders, hallucinations and/or confusion. In case of convulsive seizures, treatment with norfloxacin should be discontinued.<br>**Comment: Contains slightly less information on psychiatric disorders compared to the AU norfloxacin information. It's noted that some reactions (agitation, confusion, anxiety, depression, hallucinations, and psychotic reactions) are listed in 4.8. Given these reactions can be long lasting and significant for a patient, information on these reactions should be listed in section 4.4- this would align with the information on psychiatric reactions found in the moxifloxacin and ciprofloxacin international product information.** |
| Apo-Norfloxacin (AU) | Psychiatric Adverse Reactions<br>Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care<br>**Comment: Contains slightly more information on symptoms of psychiatric reactions.** |

**Table 31: Norfloxacin wording on antibiotic associated diarrhoea and colitis**

| Product | Safety concern: Antibiotic associated diarrhoea and colitis |
|---|---|
| Arrow-Norfloxacin (NZ) | Pseudomembranous colitis<br>The occurrence of severe and persistent diarrhoea during or after therapy may be an evidence for rarely observed pseudomembranous colitis. In such cases, therapy must be stopped immediately and a suitable therapy (e.g. vancomycin, 4 x 250 mg by oral route) has to be started. Drugs inhibiting peristalsis are contraindicated.<br>**Comment: Has less information compared to other fluoroquinolone products, consider if an update is required to align with the class warning.** |
| Apo-Norfloxacin (AU) | Antibiotic-associated colitis<br>Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with this antibiotic use (this may occur up to |

| | |
|---|---|
| | several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used<br>**Comment: Aligns with the class warning** |

**Table 32: Norfloxacin wording on tendonitis and tendon rupture**

| Product | Safety concern: Tendonitis and tendon rupture |
|---|---|
| Arrow-Norfloxacin (NZ) | Tendonitis and tendon rupture<br>Norfloxacin should not be used in patients with a present or past injury, inflammation or rupture of the Achilles tendon (see section 4.3 Contraindications and section 4.8 Undesirable effects). Tendonitis and/or tendon rupture (particularly Achilles tendon) may occur with quinolone antibiotics. The risk of tendonitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. On the appearance of tendon pain or signs of inflammation of the Achilles tendon, treatment with norfloxacin must be discontinued immediately and the patient treated accordingly. Corticosteroids should not be used if signs of tendinopathy occur<br>**Comment: Generally consistent with the class warning, however it doesn't mention that tendinitis and tendon rupture can occur within 48 hours or after several months of treatment. This is important and should be included in the data sheet.** |
| Apo-Norfloxacin (AU) | Effect on tendons<br>Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise. Achilles and other tendon ruptures that require surgical repair or resulted in prolonged disability have been reported with norfloxacin and other quinolones. Norfloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon and patients are advised to seek appropriate medical management.<br>**Comment: Contains more information that the NZ data sheet.** |

**Comment:** Norfloxacin product information from the UK and Europe could not be sourced, because the product is restricted or no longer available. The data sheet for norfloxacin should be updated with more information on prolonged, disabling and possibly persistent serious ADRs, seizures, psychiatric reactions, antibiotic associated diarrhoea/colitis, tendonitis, and tendon rupture. The MARC should consider if DRESS should be added to the data sheet noting DRESS is listed in section 4.8 of the Australian Norfloxacin PI.

#### *2.3.2.4 DRESS*

The information on DRESS is inconsistent across the class of fluoroquinolone and between individual products. Table 33 highlights whether DRESS is listed as a warning or adverse reaction in the NZ and international fluoroquinolone product information.

**Table 33: Review of DRESS in fluoroquinolone product information**

| | NZ | AU | UK | EU |
|---|---|---|---|---|
| **Ciprofloxacin** | Ipca-Ciprofloxacin Not listed<br>Aspen Ciprofloxacin Listed 4.8 | Listed 4.8 | Listed 4.8 | Listed 4.8 |
| **Moxifloxacin** | Not listed | Not listed | Listed 4.8 | Listed in 4.4 and 4.8 |
| **Norfloxacin** | Not listed | Listed 4.8 | N/A | N/A |

# 3 SCIENTIFIC INFORMATION

## 3.1 Published literature

### 3.1.1 Ellis et al, 2021, Comparative neurological safety of fluoroquinolones versus therapeutic alternatives [22]

Purpose: Fluoroquinolones are one of the most commonly prescribed antibiotic classes which have been linked with central and peripheral nervous system (CNS/PNS) adverse events. The authors of this paper sought to evaluate the safety of fluoroquinolones with regards to risk of diagnosed neurological dysfunction.

Method: Propensity score-matched cohort study using US insurance claims data of adults prescribed an oral fluoroquinolone or comparator antibiotics (azithromycin, amoxicillin +/- clavulanic acid, cefixime) from January 2000 to September 2015 for the indication's acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, uncomplicated UTI, or acute bronchitis.

The outcomes measured were CNS dysfunction and complementary PNS dysfunction up to 120 days after dispensing. Cox proportional hazards models were estimated after matching on propensity scores fitted using the variables age, sex, epilepsy, hereditary peripheral neuropathy, renal dysfunction, diabetes, gabapentinoid use, statin use, isoniazid use, and chemotherapy use.

Results: A total of 1,988,473 people were prescribed a fluoroquinolone and 4,409,572 a comparator antibiotic. Among fluoroquinolone users, the 120-day cumulative incidence of CNS dysfunction was 0.41% in era 1 (January 1, 2000 to September 14, 2004), 1.09% in era 2 (September 15, 2004 to September 30, 2015), and 0.95% in the combined cohort. For all CNS and PNS dysfunction outcomes across both eras, cumulative incidence was similar but numerically greater in the fluoroquinolone group vs. the comparator antibiotic group (Table 34).

**Table 34: Frequency and incidence rates of CNS and PNS dysfunction**

Conclusion: Fluoroquinolone users are at an increased risk of being diagnosed with acute CNS and PNS disorders relative to comparator antibiotic users prescribed antibiotics for the same clinical indication.

**Comment:** Authors identified that fluoroquinolone use compared to alternative antibiotics were associated with an increased risk of CNS and PNS dysfunction. The absolute risk is modest, and the absolute cumulative incidence of these disorders are generally low. Noting that outcomes have not been validated as this study used insurance claim data, patient adherence cannot not be confirmed and information on patient characteristics is limited.

This study suggests an increased risk associated with fluoroquinolones compared to other antibiotics when used for common infections. Noting the indications studied in this paper were the ones restricted by regulatory agencies.

### 3.1.2 Ernst et al, 2019, Comparative effectiveness of fluoroquinolone antibiotic use in uncomplicated acute exacerbations of COPD: a multi-cohort study [23]

Purpose: To review the effectiveness of fluoroquinolones when used as treatment of acute exacerbations of COPD in the outpatient setting.

Methods: Authors conducted a retrospective cohort study using healthcare databases in Canada. Patients dispensed a quinolone or alternative antibiotic were compared using inverse probability of treatment weights and propensity scoring on 30-day outcomes (repeat visits, hospitalisations, subsequent prescriptions).

Results: There were 286,866 acute COPD exacerbations amongst 203,643 individuals, the frequency of fluoroquinolone use (mostly levofloxacin and moxifloxacin), varied by province and ranged from 8% to 32% of prescriptions.

The risk of repeat ambulatory care (Figure 10) and hospitalisation within 30 days (Figure 11) was increased in patients dispensed a fluoroquinolone (OR 1.32, 95% CI 1.27–1.36) and (OR 1.52, 95% CI 1.33–1.74) respectively compared to alternative antibiotic use. There was no difference in subsequent antibiotic prescriptions.

**Figure 10: Odds ratio of repeat ambulatory care visits associated with acute exacerbation of COPD initially treated with a fluoroquinolone compared to other antibiotics.**

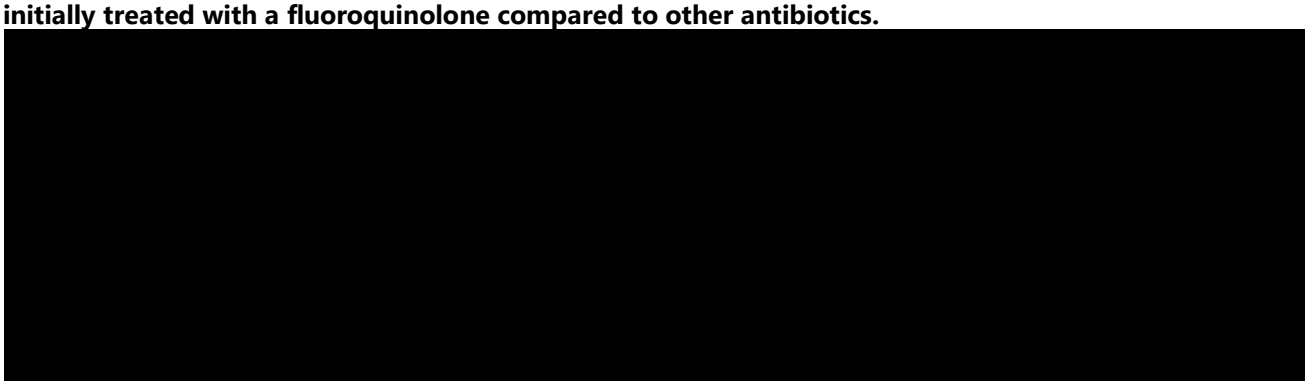

**Figure 11: Odds ratio for hospitalisations associated with acute exacerbations of COPD initially treated with a fluoroquinolone compared to other antibiotics.**

Conclusion: Treatment of apparently uncomplicated COPD exacerbations with fluoroquinolone versus non-fluoroquinolone antibiotics does not appear to be associated with improved outcomes in the following 30 days, including repeat ambulatory care visits, hospitalisation for COPD or repeat antibiotic prescriptions. These findings support current recommendations to limit the use of fluoroquinolones to more complicated patients with recurrent exacerbations or significant cardiac co-morbidity. This is especially important given the rare but severe adverse effects associated with the use of fluoroquinolone antibiotics.

**Comment:** When prescribed for an acute exacerbation of COPD this Canadian study found that fluoroquinolones were associated with an increased number of care visits and hospitalisations compared to other antibiotics (clarithromycin, azithromycin, amoxicillin, doxycycline, cefuroxime, amoxicillin/clavulanic, cephalexin). The authors identified a large cohort, and results were consistent across the different providences, patients with recent exacerbations, hospitalisations, and cardiac comorbidity were excluded.

The authors cannot confirm whether the antibiotic was prescribed for acute COPD exacerbations or other infections, information on smoking status, COPD symptom scores, bacterial susceptibility tests were not available.

### 3.1.3 Sharifzadeh et al, 2021, Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review [24]

Purpose/Method: Authors conducted a literature review to summarise reports of antibacterial/antibiotic induced DRESS reports. A total of 254 relevant cases with a definite or probable diagnosis of DRESS were identified.

Results: Of the 254 relevant cases the majority of reports were for antituberculosis medicines (107), followed by glycopeptides (46), sulphonamides (23) and penicillin-based medicines (22).

There were five reports of DRESS for fluoroquinolones (ciprofloxacin and levofloxacin) and all cases reported eosinophilia and involved the kidneys, lungs, or liver. The median latency of symptoms was 7.7 days, and all patients reported a complete resolution after drug discontinuation.

Conclusion: The authors suggest that cases of fluoroquinolone induced DRESS syndrome are mild and have a shorter latency compared to other antibiotics (tetracyclines 28.48 days, penicillin 16.53 days, aminoglycosides 31.5 days). Liver injury is less common in these cases compared to other classes of medicines.

**Comment**: Fluoroquinolones represented a small number of case reports for DRESS associated with antibacterial/antibiotic use. The authors suggest that fluoroquinolone DRESS cases are mild with a shorter time to onset compared to other classes of medicine. There were limited details for each DRESS case.

### 3.1.4 Lu et al, 2024, Antibiotic-induced severe cutaneous adverse reactions: a single-center retrospective study over ten years [25]

Purpose/Method: Authors conducted a retrospective study to analyse cases of antibiotic-induced SCARs in a tertiary hospital in China between January 2013 to January 2024.

Results: There were 354 cases retrieved of which 63 were validated antibiotic-related cases. Cephalosporins (20), penicillin's (16), and quinolones (12) were the most common triggers for SCARs.

There were two cases (one each) of DRESS reported with moxifloxacin and levofloxacin. There were five patients with SCARs triggered by other antibacterial medicines that went on to have fluoroquinolones with no recurrence of SCAR symptoms.

**Comment:** There were a small number of validated SCAR reports received over a 10 year period, the majority of reports were for β lactam antibiotics. There were two cases of DRESS from fluoroquinolones and the details from these cases were limited. A small number of patients with SCARs from other antibiotics were switched to a fluoroquinolone with no recurrence of SCARs.

### 3.1.5 Summary of case reports for fluoroquinolone induced DRESS

**Table 35: Case reports for fluoroquinolone induced DRESS**

| Author, year, title | Summary |
|---|---|
| Zhang et al, 2022, A typical presentation of moxifloxacin-induced DRESS syndrome with pulmonary involvement: a case report and review of the literature [26] | A 47-year-old female with a past medical history of hypertension, depression, and type 2 diabetes was started on moxifloxacin (dose not reported) for community acquired pneumonia. Concomitant medicines included telmisartan, flupentixol/melitracen, sertraline and metformin.<br><br>17 days after starting oral moxifloxacin they presented with ongoing fever and cough, the person was swapped to parenteral therapy and 10 days later presented with a new generalised rash and itch.<br><br>Moxifloxacin was stopped and the person was found to have leukocytic reactive changes and eosinophilia. The person was treated with antiallergic, and conventional liver-protecting treatment and symptoms resolved.<br><br>The DRESS RegiSCAR score for this case was 7. |
| Mąsior et al, 2024, DRESS syndrome: renal involvement in two cases [27] | An 85-year-old female patient (no medical history reported) was started on IV ciprofloxacin for *Pseudomonas aeruginosa* surgical site infection and six days later piperacillin/tazobactam was added. Concomitant medicines included valsartan, indapamide, bisoprolol, metformin, gliclazide, potassium. |

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|---|---|
| | 4 weeks after starting ciprofloxacin the person developed diarrhoea, low-grade fever and in subsequent days she developed an erythematous rash with oedema. She had raised CRP, WBCs (neutrophils, eosinophils), deterioration of renal function and was diagnosed with suspected DRESS.<br>The antibiotics were stopped, and the person was being treated with methylprednisolone and topical clobetasol.<br>The RegiSCAR score for this case was 6. *The second case in this article was for allopurinol |
| Mendes et al, 2023, DRESS a case report with moxifloxacin [28] | An 83-year-old male was started on moxifloxacin for acute tracheobronchitis and one week later presented with fever, mouth ulceration, a morbilliform rash which developed into erythroderma. Lab test identified leucocytosis, raised ALT, AST, CK, and myoglobin.<br>Autoimmune and viral causes were excluded, moxifloxacin was stopped and the person was treated with prednisone.<br>The RegiSCAR score for this case was 6. |

**Comment:** There are a small number of published case reports for fluoroquinolone induced DRESS. Two cases were reported with moxifloxacin and the third with ciprofloxacin.

## 3.2 Company reports

### 3.2.1 Moxifloxacin and DRESS

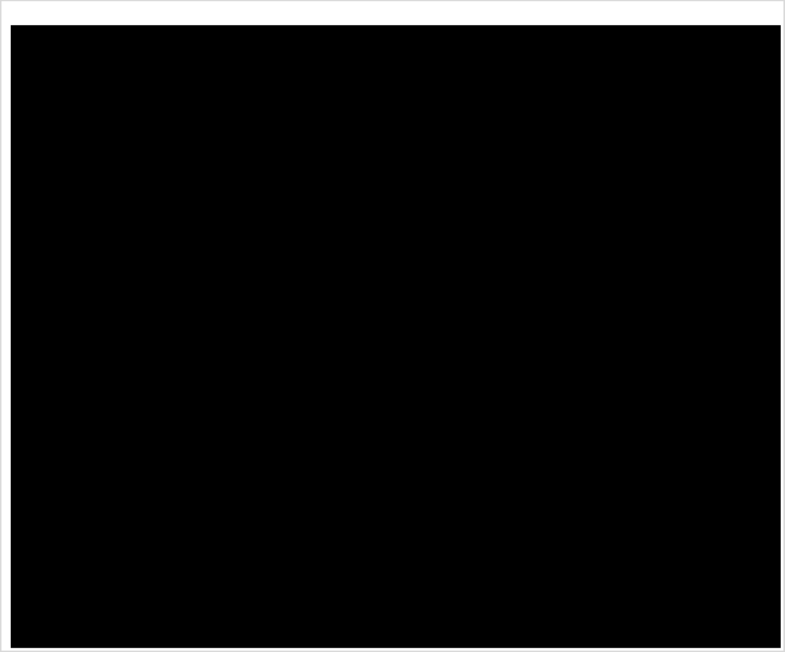
[redacted]

## 3.3 New Zealand ADR reports

Up to 7 February 2025 the New Zealand Pharmacovigilance Database holds 705 adverse reaction reports where a fluoroquinolone antibiotic was reported as the suspect medicine. Of the 705 reports, there were 536 reports for ciprofloxacin, 163 reports for norfloxacin, and 10 reports for moxifloxacin.

[redacted]

[redacted]



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*Source: New Zealand Pharmacovigilance Database. Suspected adverse reactions to medicines (accessed 17 February 2025)*

[redacted]

There is a single case report of DRESS with moxifloxacin. This case (ID136430) was reported in March 2020 and concerns a 75-year-old female who developed DRESS. The suspect medicines reported were clindamycin, vancomycin, moxifloxacin, and ceftriaxone which were taken for bacterial infections [redacted]

**Comment:** Serious adverse reactions reported with fluoroquinolones in New Zealand are consistent with the known safety profile of the medicine. No new safety concerns were identified from these cases. The frequency of prolonged, disabling and potentially persistent reactions occurring in NZ cannot be determined from this data, but international reporting rates suggest these reactions are 'rare' or have an 'unknown frequency'.

The majority of cases were reported in people aged ≥65-years, its known that increasing age is a risk factor for tendon injury. However it's possible that these individuals had more severe infections and required treatment with a fluoroquinolone.

The single case report of DRESS with moxifloxacin contained limited information. There were several co-suspect medicines which have a known association with the development of DRESS. There were no cases of DRESS reported with ciprofloxacin or norfloxacin.

**Annex 4** contains information from a group of patients from New Zealand who have experienced serious adverse reactions to ciprofloxacin.

# 4 DISCUSSION AND CONCLUSIONS

Fluoroquinolones are a class of antibiotics that have been associated with prolonged, disabling and potentially persistent (or irreversible) serious adverse drug reactions. These reactions can have a short onset time or occur several months after discontinuation and there are no proven treatments for the reactions. There are several additional safety concerns with fluoroquinolones including tendinitis and tendon rupture, aortic aneurysm and dissection, and psychiatric reactions. The MARC have previously looked at the risk of prolonged, disabling and potentially persisting adverse reactions, tendonitis/tendon rupture, and aortic aneurysm/dissection and recommended data sheet updates. Medsafe have also published *Prescriber Update* articles on fluoroquinolone safety concerns.

Due to the risk of these serious and prolonged adverse reactions regulatory agencies have taken action to restrict the use of these medicines. The most recent action was taken by the MHRA who have updated section 4.1 of the SPC to indicate that fluoroquinolones should only be used when other antibiotics commonly used are inappropriate (especially in mild to moderate infections eg acute bacterial sinusitis, acute exacerbations of COPD and uncomplicated cystitis).

A drug utilisation study in Europe/UK did not identify a significant impact of the regulatory actions on reducing fluoroquinolone use in primary care whereas a Health Canada drug utilisation study identified a

significant reduction in total fluoroquinolone prescribing from 2008 to 2022. Factors such as resistance patterns and changes in prescribing guidelines may have influenced these results. The literature suggests that use of fluoroquinolones for the indications mentioned above may have more risks compared to other classes of antibiotics.

Globally and in New Zealand there is increasing resistance to fluoroquinolones. Antimicrobial stewardship programs play a key role in ensuring the appropriate and effective use of these medicines. National guidelines on the use of antibiotics will be published this year and several resources highlight the appropriate use and safety concerns with these medicines. Medsafe and the Centre for Adverse Reactions Monitoring continue to receive ADR reports with these medicines, the most reported reaction is tendonitis- a known adverse reaction.

A review of the prescribing information highlighted several major discrepancies across the class of fluoroquinolone medicines. The sponsors should be asked to update the data sheets with the appropriate missing information. Given the recent regulatory actions by the MHRA the MARC should be asked to advise on the appropriateness of the indications, and safety information in the data sheets.

# 5 ADVICE SOUGHT

The Committee is asked to advise:

- Due to the risk of prolonged, disabling and potentially persistent serious reactions, do the indications of fluoroquinolones need to be modified to reserve use for severe infections in order to maintain a favourable benefit-risk profile?
- Whether the data sheets for fluoroquinolones need to be updated to further highlight the risk of prolonged, disabling and potentially persistent (or irreversible) serious adverse reactions and/or other safety concerns?
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*?

# ANNEXES

- Annex 1: Viatris Cipflox data sheet
- Annex 2: Data sheet comparison of section 4.4 (New Zealand and International Prescribing Information)
- Annex 3: Bayer Signal Review: Moxifloxacin and DRESS Bayer
- Annex 4: FQ joint toxicity complaint

# 6 REFERENCES

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