Medicines Adverse Reactions Committee

Meeting date	**7 December 2017**	Agenda item	3.2.1
Title	**Assessment of the potential risk of disabling and persistent musculoskeletal and nervous system adverse reactions from the use of fluoroquinolones**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Ciprofloxacin	Aspen Ciprofloxacin injection	Pharmacy Retailing
	Cipflox tablet, infusion	Mylan
	Ciprofloxacin tablet (Ethics)	Multichem
	Ciprofloxacin tablet (Rex)	REX Medical
	Ciproxin oral suspension	Bayer
	Ciprofloxacin infusion (AFT)	AFT
	Topistin infusion	AFT
Moxifloxacin	Avelox tablet, infusion	Bayer
Norfloxacin	Arrow - Norfloxacin tablet	Actavis

Funding	Ciflox, Avelox and Arrow – Norfloxacin
Previous MARC meetings	The disabling and persistent aspects of these adverse reactions have not been discussed previously.
International action	FDA (www.fda.gov/Drugs/DrugSafety/ucm511530.htm) – July 2016: FDA has approved changes to data sheets of fluoroquinolones for systemic use. These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves and central nervous system that can occur together in the same patient. Action taken/in progress by Health Canada and TGA. Evaluation in progress by EMA.
Prescriber Update	Quinolones – A Tendoncy to Rupture (September 2012)
Schedule	Prescription medicine
Usage data	See section 2.1.5
Advice sought	**The Committee is asked to advise whether:** – The data sheets should be updated regarding the risk of disabling and/or persistent adverse reactions and that more than one of these reactions can occur. – The indications for fluoroquinolones should be more clearly restricted to second line. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

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1.0 PURPOSE

The European Medicines Agency (EMA) is currently reviewing the safety of systemic and inhaled quinolone and fluoroquinolone antibiotics. The review will evaluate the persistence of serious side effects mainly affecting muscles, joints and the nervous system [1] following reports of long-lasting side effects in the national safety databases and the published literature [2].

This review follows a US Food and Drug Administration (FDA) Drug Safety Communication published in July 2016. The FDA warned about the risk of disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient [3]. A boxed warning (FDAs strongest warning) was revised to address these safety concerns.

The Drug Safety Communication also highlighted that the indications for fluoroquinolone medicines will be restricted to those patients who have no other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections. This is because the risk of these serious side effects generally outweighs the benefits in these patients.

Health Canada published a summary of a safety review on the same subject in January 2017 [4] and Australian Therapeutic Goods Administration (TGA) in September 2017 [see Annex 1]. [redacted] recommend an update the product information (PI) to communicate that some well-known side effects of fluoroquinolones (e.g. tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders), although rare, may be persistent and/or disabling. [redacted]

Considering the potential risk of serious, persistent effects and the use of fluoroquinolones in New Zealand, Medsafe considers that these safety concerns should be reviewed by the MARC.

2.0 BACKGROUND

2.1 Fluoroquinolones

Fluoroquinolones are used for a variety of infections, especially against aerobic gram-negative bacteria. Newer drugs in this class have a broader spectrum of activity including better coverage of gram-positive organisms and, for some fluoroquinolones, anaerobes. However, toxicities have been associated with some of the newer agents, which have been withdrawn from the market [5].

Resistance to fluoroquinolones has increased over time, limiting their use. Several mechanisms of resistance have been described [5].

There are three fluoroquinolone antibiotics available in New Zealand: ciprofloxacin, norfloxacin and moxifloxacin.

2.1.1 Indications

Table 1 lists systemic fluoroquinolones and their specific indications in New Zealand:

Fluoroquinolone	Indications
Ciprofloxacin	Adults: Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens in the: - lower respiratory tract - kidneys and/or the efferent urinary tract - genital organs, including adnexitis, gonorrhoea, prostatitis - abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)

	- skin and soft tissue. - bones and joints. - sepsis. - inhalational anthrax (post-exposure) - not first choice for outpatients with pneumonia due to Pneumococcus Children: - treatment of acute pulmonary exacerbation of cystic fibrosis associated with P. aeruginosa infection in paediatric patients aged 5-17 years - inhalational anthrax (post-exposure) - complicated urinary tract infections or pyelonephritis due to E.coli 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. - 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- - inhalational anthrax (post-exposure)
Moxifloxacin	Tablets and solution for infusion are indicated for the treatment of the following bacterial infections caused by susceptible strains: - Bronchitis (acute exacerbations of chronic bronchitis) - Pneumonia (community acquired) - Sinusitis (acute) - Complicated skin and skin structure infections (including diabetic foot infections) - Complicated intra-abdominal infections including polymicrobial infections such as abscesses Tablets are indicated for the treatment of the following bacterial infections caused by susceptible strains: - Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis)
Norfloxacin	- 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 - acute bacterial gastroenteritis caused by susceptible organisms - gonococcal urethritis pharyngitis, proctitis or cervicitis caused by both penicillinase and non-penicillinase producing Neisseria gonorrhoeae

2.1.2 Funding

Ciproflox tablets are currently funded by PHARMAC for the following indications:

- microbiologically confirmed and clinically significant pseudomonas infection; or
- prostatitis; or
- pyelonephritis; or
- gonorrhoea.

Arrow-Norfloxacin tablets are currently funded, but only if prescribed for a patient with an uncomplicated urinary tract infection that is unresponsive to a first line agent or with proven resistance to first line agents and the prescription is endorsed accordingly.

Avelox (moxifloxacin) tablets are funded with a Special Authority:

- prescribed by a respiratory or infectious disease specialist for tuberculosis under certain circumstances.
- prescribed by any GP for Mycoplasma genitalium when the patient has tried and failed azithromycin.

2.1.3 Pharmacodynamics

Fluoroquinolones act as direct inhibitors of bacterial DNA synthesis. Fluoroquinolones inhibit two bacterial enzymes, DNA gyrase and topoisomerase IV, which have essential and distinct roles in DNA replication. The quinolones bind to the complex of each of these enzymes with DNA. The resulting complexes, including the drug, block progress of the DNA replication enzyme complex. Ultimately, this action results in damage to bacterial DNA and bacterial cell death [5].

Resistance to quinolones is a growing, serious problem and may occur via mutations in chromosomal genes, for example genes that encode the subunits of DNA gyrase and topoisomerase IV, or via acquisition of resistance genes on plasmids. Plasmid-mediated mechanisms are almost always associated with resistance to other antibiotics [5].

In general, the first broad-spectrum fluoroquinolones (ciprofloxacin, norfloxacin) have excellent activity against gram-negative pulmonary pathogens such as *H. influenzae, Enterobacteriaceae* and with some *Pseudomonas* species. *Streptococci* are less susceptible and activity against anaerobes is poor. Atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia* species are variably susceptible but *Legionella* species are inhibited. The new fluoroquinolones, for example mofloxacin, have improved activity against gram-positive organisms, atypical pathogens and some anaerobes [6].

2.1.4 Adverse effects

The fluoroquinolones, as a class, are generally well tolerated; most adverse effects are mild in severity, self-limiting and rarely result in treatment discontinuation [7]. Adverse reactions commonly associated with fluoroquinolones are shown in Table 2:

Table 2 Common adverse reactions for fluoroquinolones.

Adverse reaction	***Range of incidence (%)***
Gastrointestinal (diarrhoea, vomiting)	*0.8 - 6.8*
Central nervous system (dizziness, headache)	*0.9 – 11*
Skin (rashes)	*0.4 - 2.1*
Blood disorders	*0.5 - 5.3*
Cardiovascular (palpitations)	*0.5 - 2.0*
Musculoskeletal	*0.5 - 2.0*

Phototoxicity or photoallergy	*0.5 - 2.1*
Serious reactions, eg, haemolytic uremic syndrome, Stevens Johnson syndrome	*<0.5*

Rare occurrences of convulsions and psychosis have also been reported. Rupture of tendons or tendonitis is a rare event associated with fluoroquinolones. Such events tend to affect the Achilles tendon, and are bilateral in 50% of cases. Predisposing factors include corticosteroid therapy (especially in the elderly), renal disease, haemodialysis and transplantation. Usually symptoms resolve within weeks, but in a small proportion of patients, they may persist for months [7]. Another risk group for tendon rupture as well as other musculoskeletal complications has been reported to be athletes in training [8].

With the identification of adverse events associated with some fluoroquinolones, newer fluoroquinolones have been scrutinised closely because of class-related adverse effects. Several of the newer fluoroquinolones have either been withdrawn from the market or had their use severely restricted because of adverse effects.

2.1.5 Usage data

The number of dispensed community-funded prescriptions in New Zealand for the fluoroquinolones are provided in Table 3. Note that data for 2016 is only complete up to the end of October.

Table 3 Number of fluoroquinolone prescriptions (tablets) dispensed at a community pharmacy

Year	Ciprofloxacin	Moxifloxacin	Norfloxacin
2010/11	95,980	106	119,348
2011/12	100,693	153	98,233
2012/13	95,743	156	89,667
2013/14	85,222	239	71,414
2014/15	82,344	251	23,687
2015/16	80,592	223	17,683
2016/17	77,669	284	12,980

Source: MoH Pharmaceutical Collection, extracted 7 November 2017

Dispensing data indicates that the use of ciprofloxacin is still high and moxifloxacin is increasing. This is of concern as community prescribing of quinolones significantly contributes to antimicrobial resistance. Note though that some of these prescriptions may be for patients just leaving the hospital.

2.2 Persistent and disabling neurological and musculoskeletal side effects

The reason for this review is the risk of persistent (prolonged) and disabling side effects including:

- tendonitis/tendinopathy (tendon inflammation or disorder)
- peripheral neuropathy (damage to or disorder affecting the nerves outside the spinal cord and brain)
- and central nervous system disorders (related to disorders of the brain)

More than one of the side effects can occur together in the same patient. The side effects are difficult to treat and may have a serious impact of the patient's quality of life.

These neurological and musculoskeletal side effects, although serious, are reported rarely (frequency 0.01%-0.1%) to very rarely (frequency <0.01%). For example, peripheral neuropathy and depression are reported rarely or with frequency unknown (see Table 4) and tendonitis and tendon rupture are reported rarely, very rarely or at frequency unknown depending on the medicine (see Table 4). However, the frequency at which these reactions become disabling and permanent or which reactions are likely to occur together as a constellation of symptoms in the same patient is not known.

2.3 NZ Data sheets and international product information

2.3.1 New Zealand

Table 4 below lists Warnings and Precautions and Adverse Effects sections of interest from the data sheets:

Table 4 Sections of data sheets covering the adverse reactions discussed.

Product (active)	Warnings and Precautions	Adverse Effects
Cipflox (ciprofloxacin) *Mylan NZ Ltd, tablets and infusion* *Data sheet date 5 March 2013* *Ciprofloxacin (AFT) Pharm infusion* *Data sheet date July 2012*	*Tendinitis and tendon rupture (predominantly Achilles tendon) sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.* *Tendonitis and tendon rupture risk is present during use and for 6 months following use of ciprofloxacin*	*Rare* *Confusion and disorientation (higher frequency if parenteral administration), Anxiety reaction, Abnormal dreams, Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide), Hallucinations (higher frequency if parenteral administration)* *Very rare* Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) (higher frequency if parenteral administration) Muscular weakness, Tendonitis, Tendon rupture (predominantly Achilles tendon)((higher frequency if parenteral administration), Exacerbation of symptoms of myasthenia gravis *Not known* *Peripheral neuropathy and polyneuropathy*
Avelox (moxifloxacin) tablets and infusion *Bayer NZ Ltd* *Data sheet date 18 May 2015*	*Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported.*	Rare: Emotional lability, Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts), Hallucinations, Peripheral neuropathy and polyneuropathy, Tendonitis *Very rare:* Depersonalisation, Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts), Tendon rupture, Gait disturbance, Exacerbation of symptoms of myasthenia gravis

Norfloxacin tablets Arrow *Data sheet date 28 April 2017*	*Fluoroquinolones, including norfloxacin, may cause tendonitis, Achilles and other tendon ruptures. The risk of these adverse effects is present during use and for 6 months following use of fluoroquinolone.* *Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Symptoms may occur soon after initiation of norfloxacin and may be irreversible.*	*Rare* *Depression, Irritability, Anxiety, Hallucination* *No frequency given* *Tendonitis, Tendon rupture, Psychic disturbances including psychotic reactions,* ***Peripheral neuropathy that may be irreversible***

Comments:

The data sheets include the actual adverse reactions per se and sometimes also mention that reactions can occur a long time after the treatment has been completed (tendon rupture). The data sheet for norfloxacin describes peripheral neuropathy, although with no frequency given, as an adverse reaction that may be irreversible.

However, except for norfloxacin and peripheral neuropathy, the data sheets do not discuss that adverse reactions can be disabling and permanent as well as occur together in the same patient. Furthermore, the data sheets do not restrict the indication for use in patients who have no alternative treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated UTIs.

2.3.2 International product information

2.3.2.1 United States

Below is the US Box Warning included in Ciprofloxacin Mylan product information. Many companies of fluoroquinolones have updated the product information, more or less meeting the requirements of FDA. In the Warning and Precautions section of the product information, the reactions are discussed in greater detail, see link:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a9a60b57-445d-4c27-bdca-5a0cbfb90502&audience=consumer

> ***WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS***
>
> - Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (see Warnings and Precautions) including:
>
> Tendinitis and tendon rupture
> Peripheral neuropathy
> Central nervous system effects
>
> - Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolones, including ciprofloxacin, in patients who experience any of these serious adverse reactions (see Warnings and Precautions (5.1). Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.
>
> - Because fluoroquinolones, including ciprofloxacin, have been associated with serious adverse reactions [see Warnings and Precautions (5.1–5.15)], reserve ciprofloxacin for use in patients who have no alternative treatment options for the following indications:
>
> Acute exacerbation of chronic bronchitis (see Indications and Usage)
> Acute uncomplicated cystitis (see Indications and Usage)
> Acute sinusitis (see Indications and Usage)

2.3.2.2 Canada

Below is the product information for ACT Ciprofloxacin (Teva Canada Ltd). Under the headline "Serious Warnings and Precautions" and in a box is the following text:

> 'Fluoroquinolones, including ACT CIPROFLOXACIN, 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.'

More information is given in the Warning and Precautions and the Adverse Reactions sections, see link: https://pdf.hres.ca/dpd_pm/00041665.PDF
Not all brands have updated their PI.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Golomb BA et al, 2015 [9]

This was a case series of four previously healthy, employed adults without significant prior medical history in each of whom symptoms developed while on a fluoroquinolone (FQ). Progression continued following discontinuation, evolving to a severe, disabling multi-symptom profile involving tendinopathy, muscle weakness, peripheral neuropathy, autonomic dysfunction, sleep disorder, cognitive dysfunction and/or psychiatric disturbance.

The first patient, who was 28 years old and otherwise in good health, was prescribed levofloxacin treatment as a precaution after sinus surgery. She had been treated several weeks before with a 7 day course of levofloxacin for a sinus infection without noted problems.

During the second FQ course symptoms emerged, including severe widespread tendon, muscle and joint pain, muscle weakness, peripheral nervous, somatic sensory, autonomic and special sense disturbances, cold extremities, gastrointestinal disturbances and central nervous system (CNS)

problems extending to cognition (including confusion), sleep and mood. The treatment was discontinued. Symptoms persisted and progressed after discontinuation, with emergence of new manifestations including fatigue, muscle atrophy, muscle spasms, fasciculations, shortness of breath and documented glucose dysregulation. The patient was bedridden throughout the year following levofloxacin use and unable to sit upright or bear weight on her feet unaided, with assistance required for feeding, bathing and toileting. Attempts at managing her pain were unsuccessful during the first year.

Patient two was an athletic 46 year old man who was treated with 750 mg/day levofloxacin for 21 days for an unconfirmed diagnosis of epididymitis. During treatment low-grade muscle aches and pains emerged which progressed after discontinuation. New symptoms emerged including fatigue, muscle weakness and atrophy, peripheral neuropathic and autonomic disturbances (tachycardia, bradycardia), CNS manifestations (cognition and mood), vision abnormalities, with gastrointestinal manifestations and intestinal motility issues. Tendinopathy emerged at 9 months which limited his life to a high extent.

He was referred to a variety of specialists and examinations but more than 5 years after the course of antibiotics this previously physically robust man remains affected with atrophy, profound muscle, weakness, chronic gastrointestinal problems, mood disturbance, recurring muscle pain and tendinopathy, and painful peripheral neuropathy.

The last two patients both had more than one course of fluoroquinolone treatment over several years, prescribed for presumed sinus infection, traveller's diarrhoea and sore throat with fever. Both patients developed muscular, neurological and psychiatric symptoms but one developed gastrointestinal symptoms in addition. The symptoms emerged during the first course but got much worse with the following courses.

The authors discuss that the series highlight the potential occurrence of serious, persistent and delayed multi-symptom adverse effects apparently triggered by fluoroquinolone use, and causing severe functional compromise and disability in previously vigorous, healthy individuals. The four patients developed new-onset symptoms during and following use of fluoroquinolones and there were no identified alternative exposures, including other medications, to which the changes were attributable.

It is suggested in the publication that mitochondrial dysfunction may be a possible mechanism for the adverse effects due to a known linking of tendon pathology (and fluoroquinolone effects) to mitochondrial dysfunction in the literature, a delayed mitochondrial dysfunction following exposure for fluoroquinolones shown in cell culture, delayed and widely variable latency to the onset of symptoms in mitochondrial dysfunction in humans and the known relation of mitochondrial dysfunction to the other fluoroquinolone affected domains.

The study bears the limitations of all case series and the authors also find the common adverse event causality criteria problematic for adverse events that persist or progress following the initial triggering insult. The authors suggest an amendment to those criteria: when a symptom occurs in the context of occurrence of one or more other symptoms already established to relate to the drug, in the presence of compatible mechanisms known to be shared by both symptoms, this boosts the causality points for that/those symptoms.

The authors conclude that fluoroquinolone use should be restricted to situations in which there is no safe and effective alternative to treat an infection caused by multidrug-resistant bacteria or to provide oral therapy when parenteral therapy is not feasible and no other effective oral agent is

available. Fluoroquinolones should be avoided for non-life-threatening, mild, moderate and uncomplicated infections.

Comments:

This was the only publication found which describes the potential disabling and persistent attributes of known adverse effects.

Mitochondrial dysfunction is one theory that has been presented to explain the discussed adverse effects.

3.2 Recommendations for use

Due to increasing worldwide resistance, also in NZ [10, 11], fluoroquinolone antibiotics should be reserved for proven or suspected infections where alternative agents are ineffective or contraindicated. The prescribing of quinolones in general practice is a serious cause for concern.

3.2.1 New Zealand

According to the NZ Formulary [12], norfloxacin is effective in uncomplicated urinary-tract infections but should be reserved for isolates resistant to empiric choices (trimethoprim or nitrofurantoin) and avoided in pregnancy.

Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae;* it should not be used for pneumococcal pneumonia. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, and septicaemia caused by sensitive organisms. It may also be used in the treatment of multi-drug resistant *Streptococcus pneumoniae*. Many staphylococci are resistant to the quinolones and their use should be avoided in staphylococcus infections, including skin and soft tissue infections [12].

Moxifloxacin should be reserved for the treatment of community-acquired pneumonia, which has failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials and as a second-line treatment for tuberculosis. Moxifloxacin is active against Gram-positive and Gram-negative organisms. Compared to ciprofloxacin, moxifloxacin has poorer activity against *Pseudomonas aeruginosa* [12].

The Best Practice Advocacy Centre (BPAC) states that fluoroquinolones should be reserved for serious bacterial infections, and used only when there is no practical alternative [10].

There are very few situations in general practice where a quinolone would be considered first-line treatment. Ciprofloxacin may be considered for the treatment of patients with pyelonephritis, travellers' diarrhoea, gonorrhoea (if sensitive) and severe cases of salmonella. Norfloxacin may be considered as a second-line option (after trimethoprim or nitrofurantoin) for recurrent UTI or for people who have failed to respond to a first-line antibiotic treatment for UTI. Quinolones should not be used in pregnant women [10].

3.2.2 United Kingdom

Public Health England (PHE) guidance on managing common infections recommends that quinolones should be avoided whenever narrow spectrum antibiotics remain effective, as they increase the risk of *Clostridium difficile*, MRSA and resistant UTIs [13].

Quinolones should, according to PHE, be used as first-line treatment only for acute pyelonephritis, acute prostatitis, epididymitis and pelvic inflammatory disease. These medicines should only be used in lower respiratory tract infections when there is proven resistance to other antibiotics [13].

3.3 International action

See also section 1.0 above.

3.3.1 European Medicines Agency - The Pharmacovigilance Risk Assessment Committee (PRAC) evaluation [1]

The PRAC (EMA) is currently reviewing the issue to determine whether there is a need to introduce new measures to minimise these risks or modify how the medicines are used. In addition, using the Eudravigilance database, PRAC is making a targeted analysis of adverse reaction reports related to the use of quinolones and fluoroquinolones, which have led to long-lasting, disabling and potentially irreversible effects. The Marketing Authorisation Holders(s) (MAH(s)) received questions, see section 3.4.1.

According to the first timeline the PRAC evaluation was to be ready for the meeting in September 2017. However it has been delayed because of outstanding issues. It is now due in December 2017.

3.3.2 US FDA evaluation [3]

The US Food and Drug Administration (FDA) Drug Safety Communication was based on FDA Adverse Event Reporting System (FAERS) data (November 1997 – May 2015) identifying 178 US cases of apparently healthy patients who took an oral fluoroquinolone for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or uncomplicated UTIs and developed disabling and potentially irreversible adverse reactions that appeared as a constellation of symptoms. The side effects occurred within hours to weeks after starting the fluoroquinolone. Only patients who reported adverse reactions lasting longer than a month and involving two or more body systems (e.g., musculoskeletal, peripheral nervous system, neuropsychiatric, senses, cardiovascular, and skin) were included in the evaluation.

The majority of cases (74%) were in patients 30 to 59 years and the mean duration of the disabling adverse reactions was 14 months, with the longest duration reported 9 years. Long-term pain of any kind was the most commonly reported symptom, with 97% of all cases reporting pain associated with the musculoskeletal adverse reactions. Many patients described how seriously the disability impacted their lives, including job loss and the resulting lack of health insurance, large medical bills, financial problems, and family tension or dissolution.

3.3.3 Health Canada review [4]

This review was published in January 2017 and included ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin when administered systemically (oral or by injection). One hundred and fifteen reports of persistent and disabling side effects associated with the use of fluoroquinolones were identified. In 78 of these reports, a probable (29 reports) or possible (49 reports) causal links could be made between the use of fluoroquinolones and persistent disability. For comparison, about 3.1 million prescriptions were filled for flouroquinolones each year in Canada.

The conclusion was that some of the known side effects (tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders) linked to the use of fluoroquinolones may be persistent and disabling in rare cases. Therefore it was recommended that the safety information for all fluoroquinolone products be updated to include information about this rare but serious risk. Canadian PI has been updated with the risk, but does not include the advice to only use fluoroquinolones for patients with acute exacerbation of chronic bronchitis, acute uncomplicated cystitis or acute sinusitis when there are no alternative treatment options (see FDA evaluation above).

3.3.4 TGA review (see Annex 1)

[redacted]

Comments:

The result of the review in the US was to update the product information for fluoroquinolones with the following:
1. Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions.
2. More than one of these reactions may affect the same patient.
3. Fluoroquinolones should be reserved for use only in patients who have no alternative treatment options for the indications acute exacerbation of chronic bronchitis, acute uncomplicated cystitis and acute sinusitis.

The result of the review in Canada was to update the product information with 1. The result of the review in Australia was [redacted]

The frequency of the adverse effects as such is noted in the adverse effects sections. No frequency is mentioned in the warning texts 1 and 2.

3.4 Company reports

3.4.1 Bayer Australia Ltd (see Annex 2)

[redacted]

[redacted]

3.5 CARM data

The Centre for Adverse Reactions Monitoring (CARM) has, up to 30 September 2017, received 605 case reports involving a fluoroquinolone. These cases were analysed for possible "Persisting Disability" criteria which resulted in 16 cases for review. Following review there were four cases which described a long-term effect and these cases are summarised in Table 5 (see also Annex 3).

Table 5 Summary of four cases with long-term adverse reactions received by CARM

Report	Date	M/F	Age	Medicine (s)	Reaction (s)	Other information
079007	Feb14	M	51	Ciprofloxacin* Mycophenolate Calcitriol Simvastatin Quinapril	Tendon rupture	
117325	Apr09	F	74	Ciprofloxacin	Tendon rupture	
120882	Jul12	M	63	Ciprofloxacin	Artralgia, joint swelling non-inflammatory dizziness, confusion, paraesthesia	

093250	Nov09	M	49	Norfloxacin	Tendon disorder, paraesthesia, dysaestesia, palpitation, pain inflammation activated	[redacted]

4.0 DISCUSSION AND CONCLUSIONS

The US Food and Drug Administration (FDA) has required that the product information for fluoroquinolone medicines for systemic use (e.g. oral and injectable) be updated. be updated with a strong warning regarding a risk of known side effects of the tendons, muscles, joints, nerves, and central nervous system becoming disabling and potentially permanent, and that more than one of these effects can occur in the same patient.

Similar action is being taken by other regulatory authorities. EMA is currently reviewing the issue.

In addition, the FDA has highlighted a restriction to only use fluoroquinolones in patients who have no other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or uncomplicated urinary tract infections. The FDA considers that the risk of these serious side effects generally outweighs the benefits in these patients. Note that the indication of acute sinusitis has been withdrawn in Europe for ciprofloxacin.

The international updates have been made based on reported cases. A literature search has revealed only one publication describing the potential disabling and persistent attributes of known adverse effects. A CARM data base search has identified 4 potential cases that fit the criteria. Two of these cases involved more than one of either the tendon, joint, muscles, CNS or a type of neuropathy.

The NZ data sheets include the actual adverse reactions per se and sometimes also mention that reactions can occur a long time after the treatment has been completed (tendon rupture). The data sheet for norfloxacin describes peripheral neuropathy as an adverse reaction that may be irreversible.

Except for norfloxacin and peripheral neuropathy, the data sheets do not include information that adverse reactions can be disabling and permanent or that more than one may occur in the same patient. Furthermore, the data sheets do not restrict the indication for use to patients who have no alternative treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated UTIs.

Due to the serious risk of drug resistance, fluoroquinolone antibiotics should not to be prescribed unless absolutely necessary. There are very few situations in general practice where a quinolone would be considered first-line treatment. This is emphasised in guidelines for use in NZ and several other countries. If followed these guidelines make the restriction in indication made by the FDA redundant. Dispensing data indicates though, that while the use of norfloxacin is rapidly decreasing in NZ, the use of ciprofloxacin is still high and the use of moxifloxacin is increasing.

The company Bayer, who market ciprofloxacin and moxifloxacin in NZ states [redacted]

[redacted]

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets should be updated regarding the risk of disabling and/or persistent adverse reactions and that more than one of these reactions can occur.
- The indications for fluoroquinolones should be more clearly restricted to second line.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. TGA report
2. Bayer's reviews [confidential]
3. CARM report

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