16 October 2018
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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Quinolone and fluoroquinolone medicinal products for systemic and inhalation use

INNs: nalidixic acid, pipemidic acid, cinoxacin, enoxacin, pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin, flumequine

Procedure number(s):

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Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

In 2016, the FDA finalised a review of disabling and potentially permanent serious side effects of systemically applied fluoroquinolones that can occur together and can involve the peripheral and central nervous system as well as tendons, muscles and joints. Based on this review, the FDA recommended in May 2016 that *"serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options."*

The safety review focussed on cases describing disabling symptoms referred to as "Fluoroquinolone-Associated Disability" (FQAD) and which must have adverse events reported from two or more of the following body systems: Musculoskeletal, Senses (vision, hearing, etc.), Neuropsychiatric, Skin, Peripheral Nervous System and Cardiovascular; and had to last 30 days or longer after stopping the fluoroquinolone.

Data from the German national database on adverse drug reactions has also revealed a number of such potential cases, where serious adverse drug reactions lasted 30 days or longer after stopping the fluoroquinolone. Moreover, publications in the past years describe such long-term adverse events.

A review of long-lasting, disabling, and potentially irreversible serious adverse drug reactions of systemic fluoroquinolones, affecting usually more than one body system had not yet been systematically evaluated for these medicinal products within previous EU regulatory procedures. While these adverse drug reactions are included in the product information of most of the authorised medicinal products in EU, the severity and the potential permanence of the effects are currently not fully addressed in the labelling of quinolones and fluoroquinolones that are authorised in the EU and need further evaluation based on all available data. Considering the nature of disabling and potentially permanent serious side effects, such review would also enable an assessment of the impact of this safety concern on the overall benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalation use and the need for adequate risk minimisation measures.

On the 1st of February 2017 the German National Competent Authority therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of quinolone- and fluoroquinolone-containing medicinal products for systemic and inhalation use and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Fluoroquinolones and quinolones (hereinafter '(fluoro)quinolones') are a class of synthetic antibacterial agents that have been used in clinical practice since 1961. The earliest substances of this class (starting with nalidixic acid) are non-fluorinated, possess only a narrow spectrum of activity against Gram-negative bacteria and have generally been replaced in clinical practices by more recent antibiotics. The later ones (starting with norfloxacin) possess an increasingly broader spectrum of activity; they are fluorinated at C-6 carbon of their basic ring structure, hence so-called

fluoroquinolones. These substances inhibit synthesis of bacterial DNA via binding to intracellular topoisomerase enzymes and forming drug-enzyme-DNA complexes.

Fluoroquinolones have been subject to several EU referral procedures. Following review at EU level, indications have been restricted for ciprofloxacin (2008), moxifloxacin (2007-2009) and levofloxacin (2012).

This pharmacovigilance referral procedure focuses on the review of the impact of long-lasting, disabling and potentially irreversible adverse drug reactions (ADRs) on the benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalation use.

While these ADRs are included in the EU product information of quinolones and fluoroquinolones, the severity and persistence of these known ADRs has not yet been systematically evaluated in the EU.

This EU review assessed the severity and persistence of these long-lasting, disabling and potentially irreversible ADRs, and evaluated the impact of these safety concerns on the overall benefit risk balance of quinolones and fluoroquinolones for systemic and inhalation use and the need for adequate risk minimisation measures.

2.2. Non-clinical aspects

The review of available non-clinical data is intended to evaluate the potential causal relationship between the use of these substances and the long-lasting, disabling, and potentially irreversible ADRs that emerged from the PRAC's safety evaluation, i.e. tendon disorders, neurotoxicity, neuropathies, phototoxicity and vasculitis. The review also takes into account data submitted by the MAHs during the procedure.

The majority of scientific publications focused on ciprofloxacin, levofloxacin and ofloxacin that are the fluoroquinolones predominantly used in clinical practice. From the available information, the PRAC considered that the potential mechanisms of the abovementioned disorders would be relevant for all (fluoro)quinolones (class effect).

Tendon disorders

The following mechanisms may be supportive of a causal relationship between (fluoro)quinolones and tendon disorders:

- Oxidative stress (ROS overproduction)

  Tendon disorders during treatment with quinolones are thought to be mediated mainly via oxidative stress (Lowes *et al.* 2009). Many non-clinical studies demonstrated quinolone-induced increase in ROS leading to cell damage. ROS overproduction and accumulation results in mitochondrial DNA damage, which triggers apoptosis by releasing caspase activating proteins into cytosol leading to impairment of tendon tissue. ROS have also direct cytotoxic effects on Extracellular Matrix (ECM) components, thus, they can oxidize amino acids in collagen, changing protein conformation, and enhance MMPs, which in turn may synergistically increase toxicity. MMPs have degrading properties, which are important in the homeostasis and response to injury of tendon tissue (Pouzaud *et al.* 2004). Moreover, it is assumed that aged tendons may have low metabolic rate and depletion of ROS scavenger systems that hinders healing (Kaleagasioglu and Olcay, 2012).

  The direct cytotoxic effects of ROS overproduction on ECM components and target cells, and the indirect cytotoxic effects mediated by enhancement of MMPs and mitochondrial dysfunction have been postulated to act in synergy as causative factors in quinolone-related ADRs.

- Mitochondrial damage

  Mitochondrial damage during quinolones treatment may be involved in tendon, cartilage and bone disorders (Stahlmann *et al*. 2013, Lowes *et al*. 2009, Barnhill *et al*. 2012). (Fluoro)quinolones inhibit activities of mitochondrial electron transport chain complexes that lead to inhibition of mitochondrial respiration and reduction of ATP production (Song *et al.* 2016). As the mitochondria are the major target of oxidative stress, quinolone-induced ROS overproduction can further result in oxidative damage to mtDNA in mammalian cells (Kalghatgi *et al.* 2013). Mitochondria participate also in apoptosis by releasing cytochrome c which starts the signalling pathway leading to activation of caspases resulting in apoptosis and lesions of affected tissues (Kaleagasioglu and Olcay, 2012).

- Inhibition of tenocytes proliferation

  In vitro studies reported that ciprofloxacin mediates inhibition of cell proliferation (Williams *et al.* 2000) and G2/M cell cycle arrest in tendon cells. Furthermore, also mitotic arrest with misaligned chromosomes has been reported (Tsai *et al.* 2009a).

- Inhibition of tenocytes migration

  Ciprofloxacin inhibits also tenocyte migration in a process that is probably mediated by inhibition of focal adhesion kinase phosphorylation (Tsai *et al.* 2009a). In this context, it was suggested that quinolones impair also healing processes through both mechanisms, i.e. inhibition of tenocyte proliferation and migration to the site of injury (Kaleagasioglu and Olcay. 2012).

- Enhanced expression of matrix metalloproteinases (MMPs)

  In general, MMPs are enzymes with degrading properties that are important in the homeostasis and response to injury of tendon tissue. It has been demonstrated that this group of enzymes participate in tendon remodelling. Using *in vitro* cell cultures, researchers highlighted the mechanism by which quinolones can selectively enhance MMPs (e.g. MMP-1, MMP-2, MMP-3, MMP-13) expression in tendon tissue that may lead to tendon ECM degradation and loss of tendon homeostasis (Lewis *et al.* 2014, Corps *et al.* 2003, Tsai *et al.* 2011) possibly making the tendon more susceptible to rupture. Animal studies also found that (fluoro)quinolones affect type I collagen metabolism leading to collagen degradation by enhanced enzymatic activity of MMPs in tendon cells at the mRNA and proteins levels (Tsai *et al.* 2011).

- Induced apoptosis

  It was demonstrated that also levels of apoptosis markers such as activated caspase-3 increased after therapeutic doses of fluoroquinolones (ciprofloxacin and levofloxacin) in a concentration- and time-dependent manner. Apoptosis was observed even at the lowest levofloxacin concentration. Apoptotic changes were further confirmed by electron microscopy and both fluoroquinolones caused typical alterations like condensed material in the nucleus, swollen cell organelles, apoptotic bodies and bleb formation at the cell membranes (Sendzik *et al.* 2005). Apoptosis markers were increased for example in rabbit meniscus (Wang *et al.* 2014), rat annulus fibrosus cells (Bai *et al.* 2014), human tendon cells or bladder cancer cells (Aranha *et al*. 2002). These side effects might result in ECM degradation and lesion of impaired tissue.

Other mechanism leading to apoptosis could be the (fluoro)quinolones-induced oxidative stress, i.e. ROS overproduction and associated mitochondrial dysfunctions (Kaleagasioglu and Olcay 2012).

- Chelation of metal ions by quinolones

  Parallels might exist in the mechanisms of chondrotoxicity and tendotoxicity of (fluoro)quinolones, since there are pronounced similarities of tendon and cartilage. Both are characterised by a low vascularization and similar matrix components, transmembrane (e.g. beta (1)-integrin receptors) and intracellular signalling proteins. The possible explanation of these toxic effects related to quinolone therapy could be the chelating properties of (fluoro)quinolones against metal ions (Khaliq *et al.* 2005, Stahlmann *et al.* 1995, Goldie *et al.* 2016). Thus, (fluoro)quinolones could be involved in tendinopathy because these drugs can interact with magnesium that is considered a regulator of the integrity of ECM. Chelation of this ion could then lead to a deficit of this important element. Additionally, epigenetic changes being mediated by iron chelation and the repression of prolyl 4-hydroxylase (P4HA1) and lysyl hydroxylase (LH1) transcription as well as inhibition of dioxygenase (HIF -1α) mRNA translation may result in tendon toxicity. (Fluoro)quinolones have been shown to be powerful iron chelators being at least as potent as the iron-chelating agent deferoxamine, clinically used for the treatment of iron overdose, hemochromatosis, and aluminium toxicity. Iron chelation by (fluoro)quinolones (i.a., by ciprofloxacin) resulted in DNA and histone hypermethylation as well as suppression of collagen prolyl hydroxylation by inhibition of jumonji domain histone demethylases (JMHD), TETDNA demethylases, and collagen prolyl 4-hydroxylases (e.g. Badal *et al* 2015).

- Ischemia and contribution of poor vascularization in tendon tissue

  It was suggested that tendon rupture may also occur due to a vascular ischemia.

Neurotoxicity

The potential for (fluoro)quinolones to induce psychotic disorders and neurotoxicity has been demonstrated in several *in vivo* studies describing neurological changes as a potential cause. Possible mechanisms behind these effects seem to be increased oxidative stress along with altered brain neurotransmitter levels.

Some of the neurotoxic effects of (fluoro)quinolones may be attributable to their binding to GABA receptors in the brain. Consequent stimulation of CNS is thus caused by (fluoro)quinolones due to prevention of normal binding of GABA with their receptors, together with decreased serotonin brain level and activation of excitatory pathways via NMDA and adenosine receptors in brain (Mandell *et al.* 2002, Kandasamy *et al.* 2012). These changes in neurotransmitter levels may lead to psychiatric disorders such as anxiety, depression, insomnia, psychosis, convulsion, etc (Ilgin *et al*. 2015, Kaur *et al*. 2016, Abdel-Zaher *et al.* 2012).

(Fluoro)quinolones-related psychiatric disorders have been also linked to oxidative stress demonstrated by significant increase of oxidative status in brain of affected animals (Kalghatgi *et al.* 2013, Duewelhenke *et al.* 2007). Increased oxidative stress markers such as MDA, NO as well as decreased intracellular GSH level and GSH-peroxidase activity in animal brain (Abdel-Zaher *et al*. 2012) have

been observed as (fluoro)quinolone-related neurotoxic effects indicating an enhanced oxidative stress and weakened antioxidant defence system, possibly leading to psychiatric disorders.

Another possible mechanism of (fluoro)quinolone-induced neurotoxic effects may lie in a significantly higher risk of apoptosis in brain cortex tissue as recently observed (Ilgin *et al*. 2015). It was also mentioned that neurons, in general, have an increased susceptibility for mitochondrial dysfunction because they are highly dependent on energy metabolism including ATP supply from mitochondria and increased demand for oxygen (Pareyson *et al.* 2013, Cogliati *et al.* 2016). Mitochondrial dysfunction may thus lead to ROS overproduction and these free radicals can further contribute to mitochondrial damage leading to many neuropsychiatric disorders.

Neuropathies

(Fluoro)quinolones-related impairments have been linked to mitochondrial diseases (Kalghatgi *et al.* 2013, Duewelhenke *et al.* 2007). Neurons have an increased susceptibility for mitochondrial dysfunction due to their metabolic requirement (Pareyson *et al.* 2013, Cogliati *et al.* 2016). Thus, mitochondrial diseases including mitochondrial dysfunction, defects in mitochondrial respiratory chain complexes, abnormalities in mtDNA replication and maintenance may further result in peripheral neuropathies (Pareyson *et al.* 2013).

Sensory neuropathy as an isolated manifestation or in setting of a neurological disorder is another possible presentation of mitochondrial diseases.

Phototoxicity

Phototoxic reactions associated to (fluoro)quinolones are considered to be a class effect. It was shown that photo-activation of (fluoro)quinolones under UVA light may result in formation and accumulation of intracellular ROS affecting cellular lipid membranes leading to inflammation (Domagala 1994). Other possible mechanism, however still closely connected to ROS overproduction, may lie in disturbing mitochondrial functions leading to apoptosis (Kaleagasioglu and Olcay 2012, Rawi *et al.* 2011).

Vasculitis

A possible explanation for (fluoro)quinolone-induced vasculitis could be related to type III hypersensitivity reaction with deposition of immune complexes and consequent damage to blood vessels by neutrophils (van Rossum *et al*. 2006). This type of delayed immune reaction seems to be elicited by IgG-mediated cytotoxic mechanisms and it is linked to T-cell. The observation of T-cell infiltrates in drug-related allergic reactions that affect the skin, liver, and kidneys, as well as drug-specific reactions found in vitro or by skin tests, strongly suggest a cell-mediated pathogenesis (Schmid *et al*. 2006). Other suggested pathophysiological mechanisms of (fluoro)quinolone-induced vasculitis are non-immune mediated reactions (Tsai and Yang 2011) including oxidative stress.

Conclusion on non-clinical aspects

Potential mechanisms of toxicity underlying the above described symptoms have been found to be multifactorial in a number of non-clinical studies. Among those mechanisms, oxidative stress and mitochondrial toxicity have been outlined in the majority of studies and MAHs´ responses. However, other possible mechanisms as highlighted above such as inhibition of cell proliferation and migration, reduced extracellular matrix, enhanced MMPs expression, apoptosis, ischemia and chelating properties of (fluoro)quinolones may be involved.

2.3. Clinical data

In general terms, (fluoro)quinolones' place in therapy is determined by international guidelines and position papers. Further information on the quinolones and fluoroquinolones' place in therapy was obtained from the EMA Infectious Diseases Working Party (see section on consultation with expert group). Due to the high number of differently worded indications across the European SmPCs and the related problem of indications that would nowadays be considered too broad or not adequately defined according to current medical terms, key efficacy data were taken into account when assessing the risk benefit balance of all existing indications.

2.4. Data on safety

Information related to the safety of (fluoro)quinolones has been obtained from different sources:

- EudraVigilance data
- Post-marketing case reports identified in literature
- Scientific literature data on disabling adverse drug reactions in quinolones
- THIN analysis

EudraVigilance data

A search was performed in EudraVigilance database to identify relevant ICRS and perform their qualitative review. The following search criteria were used:

Serious cases where one or more of the 14 (fluoro)quinolones was a suspected drug from 1995 to 2016 in the European Union with the following characteristics:[1]

1) Seriousness disabling OR
2) Reaction outcome Resolved with sequelae OR
3) Duration of at least one adverse reaction > or =30 days

The number of ICSRs returned by each of the three filters is shown in Table 1.

Table 1 - Number of ICSRs returned by EudraVigilance filters

Filter	Number of ICSRs
Seriousness - Disabling	1562
Serious - Resolved with sequelae	593
Serious - ADR duration >=30 days	165
Subtotal	2320
Number of duplicates	179
Total	**2141**

This EudraVigilance query returned a total of 2141 case reports.[2] These reports where then manually coded according to the following methodology:

1) Suspected quinolone(s) was/were marked
2) Confounding factors were identified (medication, underlying disease, other)

[2] Only EU cases were obtained; non-EU EEA cases are not included in the analysis.

3) System Organ Class(es) of relevant ADRs was/were identified
4) Disability definition: an adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life[3]; when a case report explicitly contained such information (in narrative or list of ADRs) and the length of the ADR(s) was > or =30 days the case was classified as "resulting in disability"
5) When the information about disability was not explicitly mentioned in the case report but at least one ADR lasted > or =30 days the case was classified as "potentially resulting in disability".

Results of the EudraVigilance search are summarized in Table 2.

Table 2 – Overall results of qualitative review

Type of ICSR	Not confounded	Confounded	Total
Cases resulting in disability	286	107	393
Cases potentially resulting in disability	183	88	271
Cases not resulting in disability or not potentially resulting in disability or lacking information to be evaluated			1477
Total	**469**	**195**	**2141**

Number and proportions of suspected (fluoro)quinolones are summarized in Table 3.

Table 3 - Single substance involved (cases resulting in disability)

Substance	Not confounded cases		Confounded cases	
	ICSR	%	ICSR	%
Nalidixic acid	0	0	0	0
Pipemidic acid	0	0	0	0
Cinoxacin	0	0	0	0
Flumequine	0	0	0	0
Norfloxacin	16	6	8	8
Enoxacin	1	0	0	0
Pefloxacin	2	1	1	1
Ofloxacin	27	10	4	4
Ciprofloxacin	79	28	35	33
Rufloxacin	0	0	0	0
Lomefloxacin	4	1	0	0
Levofloxacin	125	44	44	42
Prulifloxacin	2	1	1	1
Moxifloxacin	25	9	12	11
Total	**281**	**100**	**105**	**100**

[3] https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm

Subsequent statistics consider only the cases "resulting in disability" without any confounding factors (n=286).

Table 4 – Sex (cases resulting in disability not confounded)

	Males	Females	Total
ICSR	158	127	285
Percentage	55,4	44,6	100

Note: Sex unknown in 1 case

Table 5 - ICSR criteria of seriousness (cases resulting in disability not confounded)

	Death	Life threatening	Hospitalization	Disabling	Congenital Anomaly	Other
ICSR	1	2	44	255	0	73

Note 1: Percentages were not calculated as multiple criteria are often ticked simultaneously. Also, the disabling criterion was one of the filters of the search which obviously biases the distribution.
Note 2: It is apparent from the table that the EV filters "serious cases resolved with sequelae" and "serious cases with ADR duration > or =30 days" brought up only 31 cases on top of the serious disabling.

Table 6 - Number of SOCs affected (cases resulting in disability not confounded)

	1 SOC	2 SOCs	3 SOCs	4 SOCs	>=5 SOCs	Total
ICSR	181	42	20	25	18	286

Table 7 – Type of SOC(s) affected (cases resulting in disability not confounded)

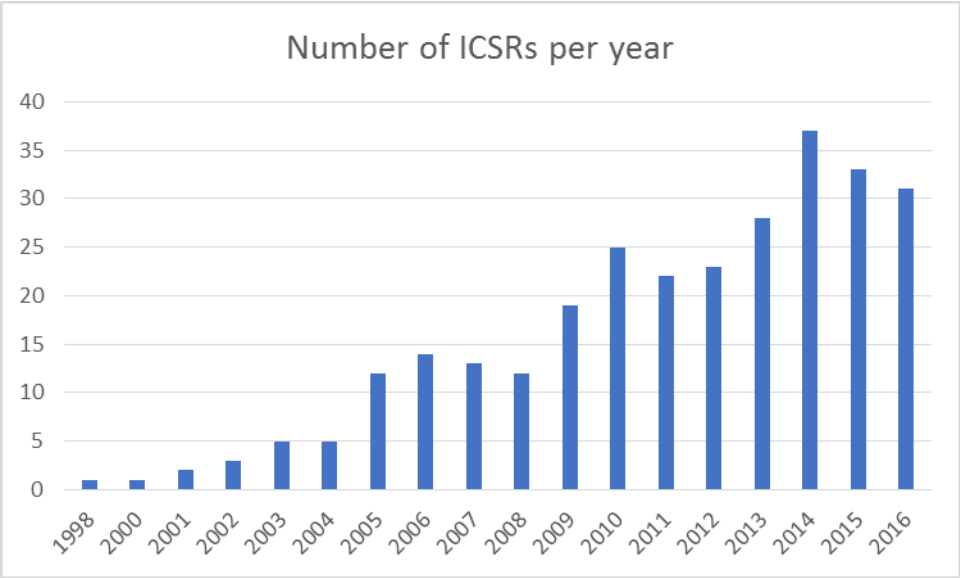
System organ class	Cases	SOC share in %
Blood and lymphatic	2	0
Immune system	5	1
Metabolism and nutrition	2	0
Psychiatric disorders	25	5
Nervous system	76	15
Eye disorders	25	5
Ear and labyrinth	10	2
Cardiac disorders	11	2
Vascular disorders	12	2
Respiratory	9	2
Gastrointestinal	18	3
Hepatobiliary	3	1
Skin and subcutaneous	13	3
Musculoskeletal	239	46
Renal and urinary	3	1
Reproductive system	2	0
General disorders	55	11
Investigations	3	1
Injury, poisoning	3	1
Social circumstances	3	1
Total	**519**	**100**

The following Table 8 show results of the analysis of PT MedDRA terms as adverse drug reactions in the group of 286 cases resulting in disability not confounded. Only PTs reported more than once were further analysed.

Table 8 – Most commonly reported PTs as ADRs

PT	Number
Tendonitis	104
Tendon rupture	69
Tendon pain	60
Arthralgia	56
Tendon disorder	43
Pain in extremity	40
Myalgia	38
Pain	32
Gait disturbance	26
Paraesthesia	23
Ageusia	16
Anosmia	16
Muscular weakness	16
Hypoaesthesia	15
Burning sensation	14
Muscle spasms	14
Depression	13
Visual impairment	13
Tendon discomfort	12
Tinnitus	12
Dysgeusia	11
Dizziness	10
Fatigue	10
Nausea	10
Oedema peripheral	10
Sleep disorder	10

Figure 1 - Number of incoming ICSRs per year (resulting in disability not confounded)



In summary, the targeted search of EudraVigilance database retrieved 2,320 (fluoro)quinonole-related cases of interest (including 179 duplicates) out of which 393 cases resulted in disability (286 were not confounded and 107 were confounded by other factors). A detailed qualitative analysis performed on the 286 not confounded cases yielded the following characteristics of the reported cases and ADRs:

- Levofloxacin, ciprofloxacin, ofloxacin, moxifloxacin, and norfloxacin were the most commonly involved substances
- Males were slightly more affected than females (55:45)
- From age of 30 to 89 years the case distribution was approximately even
- In about one third of cases the (fluoro)quinolone was indicated for a mild or potentially mild illness
- ADRs from SOCs musculoskeletal (46 %), nervous system disorders (15 %), and general disorders (11 %) were most commonly reported. An alternative classification of the ADRs yielded the following proportions: tendinopathy 24 %, pain 18 %, nervous system disorders 12 %, muscle (and bone) disorders 11 %, sense disturbances 10 %, general disorders 9 %, arthropathy 8 %, and psychiatric disorders 7 %.
- One SOC was affected in 63 % of cases, two SOCs in 15 % of cases, and three or more SOCs in 22 % of cases

Link between frequency of ADR and exposure

The reporting rate (proportion of cases that are reported out of the total of actual cases) of the "cases resulting in disability" is unknown. However, thanks to the exposure data, the yearly number of ICSRs can be linked to (fluoro)quinolone consumption to get a better idea of the scale of the problem. The calculation is presented in Table 26 for 2014 and in Table 27 for the last five years (2012-2016) using extrapolated data (constant consumption based on year 2014). The rate of incoming ICSRs (resulting

in disability not confounded) per unit of consumption (1 million DDDs) is calculated using two independent data sources: (1) the JIACRA report and (2) the NUI exposure data for a group of EU representing about two thirds of EU population.

Table 9 - Number of reported cases (resulting in disability not confounded) and exposure in 2014

	In countries with NUI exposure data	In EU
Number of cases	26	37
Exposure in millions of DDDs from NUI	238	-
Exposure in millions of DDDs from JIACRA	-	342
No. of reported cases per 1 million of DDDs	0,109	0,108

Note: Receive date of the case report used to determine year

NUI exposure data from BE, BG, CZ, DE, DK, ES, FI, FR, IT, LT, LV, NL, PT, SE, SI, SK

Table 10 - Number of reported cases (resulting in disability not confounded) and exposure 2012-2016 (5 years)

	In countries with NUI exposure data	In EU
Number of cases	120	152
Exposure in millions of DDDs from NUI	1188	-
Exposure in millions of DDDs from JIACRA	-	1710
No. of reported cases per 1 million of DDDs	0,101	0,089

Assumption: exposure for 2012-2016 obtained by multiplying 2014 exposure by 5

Note: Receive date of the case report used to determine year

NUI exposure data from BE, BG, CZ, DE, DK, ES, FI, FR, IT, LT, LV, NL, PT, SE, SI, SK

All four calculations indicate that the rate of incoming ICSRs (resulting in disability not confounded) is about 1 per 10 million DDDs.

Post-marketing case reports identified in literature

A number of published case reports relevant to the topic of long-lasting, disabling and potentially irreversible ADRs associated with the quinolones use were identified both from EU and non-EU area.

The level of detail captured by these published case reports is mostly higher than in the cases reported directly to EudraVigilance. In terms of tendinopathies, case series included, there have been hundreds of published cases with time lag between the first dose and the onset of symptoms ranging from 2 hours to several months and the durations of disability ranging from days to more than one year. In terms of peripheral neuropathy, case series included, dozens of cases have been published with the

duration of disability ranging from days to years. Multiple cases of long-term serious adverse reactions to (fluoro)quinolones have also been published by physicians working in the fields of psychiatry, ophthalmology, dermatology and other specialties. At least four cases of patients with ADRs affecting several organ systems simultaneously have been published as well. Characteristics of a large majority of these published cases reveal a pattern that fits the descriptions of unpublished cases reported directly to EudraVigilance from the EU territory.

Scientific literature data on disabling adverse drug reactions in quinolones

A summary of data on disabling adverse drug reactions related with quinolones use, obtained from scientific literature data is presented below.

Musculoskeletal disorders

Many studies have highlighted the relationship between (fluoro)quinolones treatment and musculoskeletal disorders such as tendonitis, tendon rupture, cartilage damage, arthralgia, muscle pain, etc. Tendinopathy has been recognized as an uncommon, but potentially disabling adverse effect of quinolones. (Fluoro)quinolones can easily penetrate tissues; myotendinous junction may thus predispose tenocytes to elevated drug exposure. Concentrations of quinolones in tissues often exceed those in plasma (Horn *et al.* 2016).

The possible mechanisms of (fluoro)quinolones induced musculoskeletal disorders are multifactorial, mainly via mitochondrial damage and oxidative stress, but also other mechanisms such as inhibition of cell proliferation and migration, reduced extracellular matrix, enhanced MMPs expression, apoptosis, ischemia and chelating properties of quinolones, might be involved (see Non-clinical section).

A typical feature of (fluoro)quinolone-induced tendinopathy is the wide range of occurrence of the symptoms, sometimes very delayed. Indeed, the timeframe of the symptoms occurrence ranged from 2 hours after the 1st dose to 6 months after the treatment discontinuation (Khaliq and Zhanel 2003). There was also a report of tendon disorders occurring 18 months after the (fluoro)quinolones exposure (van der Linden *et al*. 2001). (Fluoro)quinolones have been found to induce delayed mitochondrial toxicity and cytotoxicity, providing an evidence for reported occurrence of delayed (fluoro)quinolones AEs. Mitochondrial injury may induce oxidative stress as mitochondria are the leading source as well as target of intracellular free radicals. Oxidative stress may in turn produce more mitochondrial damage. This can create a cycle of oxidative stress and mitochondrial injury that can be self-sustaining or progressive, leading to the emergence of new symptoms as clinical detection thresholds are reached (Wefers *et al*. 2009, Golomb *et al*. 2015 Kaleagasioglu and Olcay 2012).

Adikwu *et al*. (2012) performed a comprehensive survey and review of literature on reported ciprofloxacin induced chondrotoxicity and tendinopathy in humans and animals. It was observed that ciprofloxacin is a potential inducer of chrondrotoxicity and tendinopathy which could be potentiated by coadministration with corticosteroids.

Data from the literature suggest that the course of (fluoro)quinolone-induced tendon injury might be prolonged and manifestation of tendon disorders might persist for several weeks or months. The rehabilitation process require less aggressive approach than other types of tendinopathies and the outcome in some patients may result in permanent disability (Bidell and Lodise 2016, Stahlmann *et al* 2010, Lewis *et al* 2014, Baombe 2016). The review of 98 case reports of tendon injury associated with (fluoro)quinolone use showed that the time for recovery ranged from 2 to 600 days, median: 38,5 days. Several reports described recovery as "prolonged" and in 10% of patients sequelae were reported (Khaliq and Zhanel 2003).

Arabyat *et al.* (2015) reviewed reports in the Food and Drug Administration's adverse event reporting system for fluoroquinolone-associated tendon rupture. From the 2495 FAERS reports of tendon rupture associated with currently approved fluoroquinolones 1555 were associated with levofloxacin, 606 with ciprofloxacin, 230 with moxifloxacin, 70 reports with ofloxacin and 30 with norfloxacin as well as 4 with gemifloxacin. Almost all the cases were considered serious and the most commonly reported outcomes were hospitalisation (35,6%) and disabling events (20,8%). Summarising all FQ, if indication was known, the most cases occurred with the indication infection of the respiratory tract, there especially in the indication sinusitis followed by other infections including cystitis, diverticulitis, epididymitis, prostatitis, and unspecified bacterial infections.

Stopping treatment immediately after the onset of first symptoms of (fluoro)quinolones therapy does not ensure preservation of tendon integrity, as the tendon may rupture or become symptomatic months after the end of the treatment (Lewis *et al* 2014). In case of tendon rupture, immobilisation from 6 weeks to 6 months is recommended (Tsai and Yang 2011).

Some authors suggest that myalgia may be the most common adverse reactions associated with (fluoro)quinolones use (O-Lee *et al*. 2005). They usually manifest one week after the initiation of (fluoro)quinolones therapy typically as a diffuse pain with or without weakness and often resolve within 1 to 4 weeks after the discontinuation of the medication, symptoms that persisted more up to 6 months have been also reported.

Although the occurrence of tendon rupture is rare this risk should be considered in the risk-benefit assessment especially when the indication for use is the treatment or prophylaxis of an uncomplicated infection.

Psychiatric disorders

CNS effects of (fluoro)quinolones correlate with its binding to GABA receptors in the brain. This interaction might prevent normal binding of GABA with their receptors causing stimulation of CNS. (Fluoro)quinolones may also activate excitatory pathways via NMDA and adenosine receptors in brain. CNS symptoms are thus manifested and can explain the pathogenesis of psychiatric disorders such as anxiety, depression, insomnia, psychosis, etc. (Mandell *et al*. 2002, Kandasamy *et al*. 2012). The altered brain neurotransmitter levels along with oxidative stress leading to anxiety, depression and convulsions have been observed in some animal studies demonstrating the possible mechanisms of (fluoro)quinolones-associated neurotoxicity (Ilgin *et al*. 2015, Kaur *et al*. 2016, Abdel-Zaher *et al.* 2012). As mentioned above, (fluoro)quinolones-related psychiatric disorders have been linked to oxidative stress as well as mitochondrial diseases (Kalghatgi *et al.* 2013, Duewelhenke *et al.* 2007). It was mentioned that neurons have an increased susceptibility for mitochondrial dysfunction as they are highly dependent on energy metabolism including ATP supply from mitochondria and increased demand for oxygen (Pareyson *et al.* 2013, Cogliati *et al.* 2016). Fattal *et al*. (2006) identified 19 confirmed case reports of mitochondrial diseases/disorder with comorbid psychiatric problems, including bipolar disorder, major depressive disorder, psychosis, anxiety disorders, and personality changes. The most common physical findings were fatigue, muscle weakness with or without atrophy, and hearing loss. A review of literature performed by Anglin *et al.* (2012) showed that the most common psychiatric presentations in the cases of mitochondrial disorders included mood disorder, cognitive deterioration, psychosis, and anxiety. All these evidences suggest that quinolones-mediated mitochondrial dysfunctions could explain neurological and psychiatric reactions.

Review of cases of psychiatric adverse effects from the French pharmacologic surveillance database carried out by Doussau de Bazignan *et al*. (2006) identified and reviewed 590 cases, with the most frequently reported ADRs of confusion (51%), hallucinations (27%) agitation (13%), and delirium

(12%). There were also 9 cases of mania, 7 cases of mental disorders, 6 cases of depression and 6 cases of personality disorders. 21,7% of cases were severe, necessitating hospitalisation or prolongation of hospital stay.

Despite the fact that CNS-associated adverse reactions are well recognised, published information regarding the duration and outcome of neuropsychiatric ADR are scarce. In the review by Doussau and Bazignan (2006), the outcome was completely resolution for 88,5% cases, whereas in 9,5% the reaction was ongoing or unknown. There were 11 deaths recorded; according to the author, only one of them was possibly associated with the psychiatric ADR. Review of psychiatric and neurological adverse drug reactions carried out by Tomé and Filipe (2011) analysing 145 individual case reports indicates that in the majority of cases, patient recovered without sequelae and the events usually disappeared after drug discontinuation. None of the reported ADRs resulted in disability; however, 51% of the cases did not contain information on the seriousness criterion. Several published individual case reports were identified where the aspect of the long-term persistence and disability might be captured.

Neuropathies (peripheral, sensory)

Similarly, to psychiatric disorders, (fluoro)quinolones-related neurotoxicity that may lead to peripheral or sensory neuropathies has been linked with mitochondrial diseases (Kalghatgi *et al.* 2013, Duewelhenke *et al.* 2007, Pareyson *et al.* 2013).

One of the first publications discussing the possible peripheral disturbances was the review of 37 ADR reports from the database of Swedish Drug Information System performed by Hedenmalm and Spigset in 1996. Subsequently, publications opposing to the current assumption that neuropathies associated with the quinolones are mild and reversible after the drug discontinuation emerged. In the review of 45 cases suggestive of peripheral neuropathy symptoms published by Cohen (2001), 93% of patients experienced symptoms in multiple organ systems. The duration of the symptoms was longer than 3 months in 71% of cases and longer than 1 year in 58% of cases. 27% of the cases exceed time duration of 2 years and one case continued more than 6 years. Severity of the symptoms led 11 patients to seek medical assistance at emergency departments.

Francis and Higgins (2014) in their case report and literature review highlight the challenge of diagnosing the quinolones associated peripheral neuropathy as the broad spectrum of diffuse and confusing symptoms might be present. The same authors conclude that the peripheral neuropathy associated with quinolones administration can be severe, debilitating and permanent.

Analysis of FAERS pharmacovigilance data performed by Ali (2014) stresses the link between the quinolones and peripheral neuropathies and showed potential association between the quinolones and more severe forms of nerve damage such as Guillain-Barre syndrome. Peripheral neuropathy was recorded in 539 reports out of all 46 257 adverse event reports for systemic quinolones, and Guillain-Barré syndrome was recorded in 48 reports (9% of peripheral neuropathy reports). None of the patients who experienced peripheral neuropathy or Guillain-Barré syndrome was recovered from the event, and the vast majority of peripheral neuropathy events were of serious outcomes (including all Guillain-Barré syndrome reports). Among serious events, six (1.2%) contributed to patient death, and 137(27.8%) lead to physical disability. The author concludes that unless the benefit of quinolones therapy outweighs the risk of peripheral neuropathy, alternative antibacterial agents for which peripheral neuropathy is not an identified or potential risk are recommended.

Skin disorders

With regard to the long-lasting or disabling potential of this ADR, only limited data are available, most of them being the individual case report publications.

Leukocytoclastic vasculitis (LCV) is uncommon but potentially serious adverse reaction, its clinical course is usually benign, however fatal case associated with ofloxacin was reported (Pace *et al*. 1989). Because of the rare nature of this ADR, no specific recommendations for the management of LCV exist (Morgado *et al*. 2016)

Generally, in drug induced LCV, resolution of the symptoms follows shortly after the withdrawal of offending agent within the days to weeks without the need of treatment. Patient with the joint involvement might benefit from NSAIDs treatment; patient with chronic or systemic disease might require prednisolone treatment (Martinez -Taboada *et al*. 1997).

THIN analysis

The EMA conducted two population-based nested case-control studies to assess the risk of tendon rupture and peripheral neuropathy with systemic exposure to fluoroquinolone (FQ) antibiotics. The cohort consisted of adults aged 18 years or over defined from The Health Improvement Network (THIN) between January 1, 1999 and December 31, 2015 who were issued at least one prescription of co-amoxiclav or fluoroquinolone antibiotic product with a systemic route of administration.

The results of the study on tendon rupture revealed that a history of prior tendon rupture and concomitant exposure to corticosteroid therapy increase the risk of any tendon rupture. Cumulative FQ exposure during the evaluated risk periods appeared to be associated with a duration-related relative increase in the risk of tendon ruptures. Duration of use longer than 10 days was associated with risk estimates of Achilles tendon rupture of 4.52 (95% CI 2.23-9.14) as compared to estimates of 2.82 (95% CI 1.77-4.51) if duration of use was ≤10 days. It was additionally shown that the Achilles tendon is the most frequent affected tendon.

The results of the study on peripheral neuropathy indicate that there may be an increased risk of peripheral neuropathy associated with intake of fluoroquinolone antibiotics (ciprofloxacin, moxifloxacin, levofloxacin, norfloxacin and ofloxacin).

2.4.5. Discussion on demonstrated risks

(Fluoro)quinolones cause long-term, persistent, potentially irreversible adverse drug reactions that can substantially disrupt patients' daily activities, i.e. they are disabling. These ADRs are already present in most European product information of (fluoro)quinolones. Their disabling potential presents an important harm for patient suffering from mild/non-serious infection or uncomplicated forms of serious infections that were otherwise healthy or nearly healthy.

Long-lasting, disabling and potentially irreversible ADRs affecting musculoskeletal and peripheral nervous system

Assessment of the post-marketing spontaneous and literature data together with the evaluation of available non-clinical and clinical information related to the possible underlying mechanisms of long-lasting, disabling and potentially permanent ADRs provided enough evidence to support causal relationship between the (fluoro)quinolones and potentially disabling ADRs affecting musculoskeletal and peripheral nervous system such as musculoskeletal pain, arthralgia, myalgia and tendinopathies

including tendinitis and tendon rupture, peripheral neuropathy, polyneuropathy, paraesthesia, dysesthesia, etc.

Analysis of EudraVigilance data showed that out of all cases identified as resulting in disability, ADRs from SOCs Musculoskeletal and Nervous system disorders were most commonly reported. Out of 286 cases identified as resulting in disability, in 239 cases (46%) musculoskeletal and in 76 cases (15%) nervous system was affected. Most reported adverse reactions were tendon disorders including tendonitis, tendon rupture, arthralgia, myalgia and pain in extremity as well as neurologic/psychiatric disorders including impairment of senses (e.g. peripheral sensory neuropathy with hypaesthesia, paraesthesia, dysgeusia and anosmia, tinnitus, deafness/hypoacusis and dizziness, aphasia, thinking disturbance and memory loss). These findings are consistent with the data available from scientific literature.

Regarding the neurological disorders, most of the information on the long-lasting, disabling and potentially irreversible character of ADRs already known for (fluoro)quinolones is available from analysis of spontaneously reported data (Hedenmalm and Spigset 1996, Cohen 2001, Ali 2014).

Taking into consideration the limitations inherent to the evaluation of spontaneous data, these publications due to the number of evaluated data offer valuable insight into the nature of ADRs related to peripheral nervous system. Francis and Higgins (2014) in their literature review explicitly suggest that peripheral neuropathy associated with (fluoro)quinolones use can be severe, debilitating and permanent.

Potential irreversibility of peripheral neuropathy was already discussed within the PSUSA procedure for moxifloxacin (2017). Based on the information reviewed in this PSUSA (including 50 reports of peripheral neuropathy although displaying limited information on irreversibility due to lack of relevant information over the long-term follow-up, hundreds of publications on the potential for irreversible neuropathies caused by a huge variety of drugs including fluoroquinolones dealing also with the potential mechanisms including mitochondrial toxicity, nonsystemic vasculitis, and others) PRAC considered that section 4.4 of the SmPC should be amended to emphasise the need of treatment discontinuation at first signs of peripheral neuropathy in order to prevent the development of irreversible conditions. Additionally, PRAC considered that information for patients regarding the location of symptoms should be added.

CNS effects / Psychiatric disorders

(Fluoro)quinolones effects on CNS are well recognised being the 2nd most common reported adverse drug reactions reported in association with these medicinal products. Also, non-clinical evidence of quinolones neurotoxicity is available and their potential role in pathogenesis of psychiatric disorders such as anxiety, depression, insomnia, psychosis and others, was described (Mandell *et al*. 2002, Kandasamy *et al*. 2012).

However, data on the long-lasting, disabling and potentially irreversible ADRs related to the CNS has not been studied systematically and most of the information from the scientific literature can be found in publications analysing spontaneous data (Cohen 2001, Doussau de Bazignan 2006, Kaur 2016).

Analysis of the EV data showed that ADRs from psychiatric disorders SOC were reported for 25 cases resulting in disability (5% of all cases). SOC Psychiatric disorders (together with SOC Eye disorders) were the 4th most commonly reported SOC. The brief examination of the PTs reported for these 25 cases revealed that sleeping disorders ("sleep disorder", "insomnia" and "poor quality of sleep") were reported in 19 cases (76% of cases from psychiatric disorders), depression ("depression", "depressed mood") was reported in 13 cases (52%) and "anxiety" in 8 cases (32%).

In the FDA review of disabling and potentially permanent serious side effects neuropsychiatric ADRs counted for 68% of 178 cases identified as relevant for the safety review (review (http://wayback.archiveit.org/7993/20170113234645/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM467383.pdf). Of note, in cases where insomnia, depression or some other ADR where reported to be the consequence of pain, these secondary ADRs were not included into the analysis. Based on this review, the FDA included in their final safety communication quinolone-induced central nervous system ADRs to the group of ADRs with disabling and irreversibility potential.

Considering all available information including the non-clinical evidence, there is a reasonable amount of evidence pointing to the causal association between (fluoro)quinolones and long-lasting, disabling and potentially irreversible reactions that manifest as CNS effects and psychiatric disorders.

2.4.5.1 Uncertainties about risks

Risk factors/confounders

There is still some uncertainty about risk factors related directly to the assessed long-lasting, disabling and potentially irreversible ADRs.

The risk of quinolone-induced tendinopathy can be increased by underlying disease or co-administrated medicines. A review of Mandell et al. (2002) mentioned that predisposing factors for tendinopathy are corticosteroid therapy, advanced age, renal disease, haemodialysis and transplantation. These findings are consistent with Horn et al. (2016) that also proposed other risk factors such as rheumatic disease, gout, high doses of quinolones, male gender and age over 60 years. Sport activity and history of musculoskeletal disorders should be also considered (Tsai and Yang, 2011). Strenuous physical activity, during or after the therapy of quinolones may logically conduce to tendon injury. Moreover, Lewis and Cook (2014) suggest that physical exercise can alter the production of matrix metalloproteinases which can adversely alter the structure of the extracellular matrix of tendons. In early investigations with pipemidic acid it was assumed that joint damage would involve only those joints subjected to static stress during therapy. However, subsequent studies demonstrated that lesions can also develop in immobilized joints (von Keutz iet al. 2004).

Based on the different and multiple potential mechanisms of toxicity evaluated for (fluoro)quinolones (see non-clinical section) some uncertainties remain on possible risk factors such as BMI for tendon ruptures as shown in the THIN study "Association between systemic fluoroquinolone exposure and tendon rupture: population-based nested case-control study". Concomitant medication may also impair mitochondrial function or underlying history of mitochondrial impairment. The latter has been shown as risk factor for ototoxicity of aminoglycosides (Tang *et al.* 2002). Additionally, the interplay of the different mechanisms of toxicity and their individual contribution to the overall effect of long lasting adverse reactions has not yet been elucidated.

Several studies focusing on (fluoro)quinolone-related neuropsychiatric disorders such as peripheral neuropathies, delirium, suicidal ideation, chorea or hemiballism highlighted the risk factors in the context of neurotoxic effects. These factors are high dosage of (fluoro)quinolones, female gender, young age (<45 years), renal failure and pre-existence of central nervous system disease (Tomé and Filipe 2011, Hedenmalm and Spigset 1996, Ali 2013). Furthermore, drug interaction between NSAIDs, theophylline, caffeine and ciprofloxacin have been identified as important factors for toxicity (Ilgin *et al.* 2015). It has also been shown that co-administration of the NSAID fenbufen enhances the binding of quinolones to GABA receptors leading to clinically significant symptoms (Mandell *et al*. 2002).

In the setting of renal dysfunction as well as in the elderly, there is a risk of high blood levels of quinolones that could lead to a higher risk of the assessed ADRs. Systematic steroid therapy was highlighted by some authors as one of the leading confounded factors that contributed to the risk of potential long-lasting tendon disorders.

Risk factors associated directly with (fluoro)quinolone-induced mitochondrial dysfunction possibly leading to multifactorial ADRs, as mentioned in non-clinical part, have not been extensively discussed in scientific literature so far, probably due to the low reporting rate of long-lasting, disabling or potentially irreversible ADRs. Golomb et al. (2015) mentioned concomitant medication such as chemotherapy, HIV protease inhibitors, statins and amiodarone that can amplify the risk of quinolones mitochondrial toxicity, however, these conclusions are limited by the low number of case reports assessed within this study. A recent publication by Michalak et al. (2017) summarises the underlying mechanism of so called "Fluoroquinolone Associated Disability" and tries to identify possible treatment approaches, however it does not provide any discussion about risk factors linked directly to the underlying mechanism of long-term, disabling or potentially irreversible ADRs.

Time to onset

Delayed occurrence of the symptoms is considered a typical feature of quinolone-induced tendinopathies and the time frame described in scientific literature ranged from 2 hours after the 1st dose to 6 months after the treatment discontinuation (Khaliq and Zhanel 2003). A report of tendon disorders occurring 18 months after the quinolones exposure has been published (van der Linden *et al.* 2001).

There is also non-clinical evidence showing that (fluoro)quinolones induce delayed mitochondrial toxicity and cytotoxicity (Wefers *et al.* 2009, Golomb *et al.* 2015, Kaleagasioglu *et al.* 2012).

Differences within class

Due to the assumed low frequency of the ADRs in question it is not possible to determine to what extent some (fluoro)quinolones induce these long-lasting, disabling and potentially irreversible ADR more than others. As it is apparent from exposure data and the analysis of the 286 not confounded disabling cases, the five substances with the highest consumption (ciprofloxacin, levofloxacin, ofloxacin, norfloxacin, moxifloxacin) are the same substances that are most commonly mentioned as suspected. The potential of other (fluoro)quinolone agents, namely cinoxacin, flumequine, pipemidic acid, and rufloxacin to induce the same disabling ADRs cannot be ascertained, due to low exposure to those substances, but it cannot be ruled out.

Frequency per unit of exposure

These long-lasting, disabling and potentially irreversible ADRs have been reported in the EU with the frequency of about 1 spontaneous case report (resulting in disability not confounded) per 10 million of DDDs (defined daily doses). Given the relatively low number of incoming case reports in comparison with the high exposure, actual frequency of these ADRs cannot be determined from available data. The signs and symptoms that result in (fluoro)quinolone-related disability are highly varied and may span several organ systems in one patient. Standard analyses of drug safety in clinical trials as well as post-marketing monitoring tools are not well suited to capture long-term impact of these signs and symptoms on daily-life activities of individual patients. In addition, the public attention directed at this safety issue which is enhanced by the use of the Internet and social media further complicates any attempts to reach a reliable estimate of the frequency. However, taking into account the yearly exposure of about 350 million DDD in the EU as well as average treatment duration and underreporting it is safe to assume that these ADRs are most likely very rare (<1/10,000).

Recommendation for further research

Relevant stakeholders, including academia and MAHs, are encouraged to perform further research that would further characterize these disabling adverse drug reactions. The research should focus on current gaps and uncertainties in knowledge, including but not exclusive to, risk factors associated with these specific ADRs, ADRs to fluoroquinolones in the past, treatments for the ADRs, identification of possible biomarkers to predict these ADRs and underlying mechanisms of action that could lead to the respective reactions.

3. Expert consultation and Stakeholders input

The PRAC requested several consultations with different stakeholders during this review in order to collect all the available current information from different sources.

3.1. Public hearing

On 13 June 2018, the European Medicines Agency (EMA) held a public hearing on quinolone and fluoroquinolone antibiotics to hear the views of patients and the general public on the persistence of side effects reported with this group of medicines.

Sixty-nine participants attended it in person or called in by telephone, including 40 patients and patient representatives, 14 healthcare professionals and academics, 13 representatives from pharmaceutical industry as well as members of the media. Other members of the public who could not attend sent submissions in writing, which were equally taken into account during the review.

During the hearing, patients described many serious problems they have experienced with a time relationship to the use of a (fluoro)quinolone containing product and which led to their sever disability.

The clinical presentation of the risks associated with (fluoro)quinolones, described by the majority of public hearing participants, was in general consistent with the characteristics of musculoskeletal and peripheral and central nervous system ADRs identified in EudraVigilance database and scientific literature during the referral procedure. The common features presented in all the personal histories were the prolonged duration of the adverse drug reactions related to the (fluoro)quinolones use ranging from months to years, affection of multiple body systems and multiple sides for each, and significant disturbance in everyday-life activities due to the severe fatigue and pain associated with the musculoskeletal and nervous system impairments.

A call for more information to be included in the PIL and SmPC was noted. This is in order to increase the awareness of both healthcare professionals and patients about the possible prolonged or persistent character of (fluoro)quinolones associated ADRs. Warning of not using (fluoro)quinolones in patients who have experienced any serious ADR in the relation to (fluoro)quinolones in the past except for life threating infections, were also requested.

The call for significant restriction of (fluoro)quinolones use, i.e. only for life threatening/severe infections, as a last option, hospital use etc., was raised by the majority of general public participants. A striking pattern of unjustified use in self-limited or non-bacterial infections was identified repeatedly in individual interventions; the absence of proper testing of infectious agent or bacterial sensitivity was highlighted.

The majority of the patients highlighted an unawareness of healthcare professionals of the possibility that these long lasting/persistent reactions were related to (fluoro)quinolones use and that no warnings were given to the patients. Healthcare professionals were generally unaware of the broad range and severity of possible symptoms, with exception of Achilles tendon disorders. An information campaign was considered necessary to be conducted at the end of this procedure to inform both patients and health care professionals on this specific risk.

Awareness of some cases of exacerbation and prolongation of existing ADRs due to systemic (fluoro)quinolones following the subsequent use of topical (fluoro)quinolones without first-hand personal experience was mentioned at the margins of patients' interventions. Although topical (fluoro)quinolones were not included in the scope of this referral procedure, a further search in EudraVigilance on possible cases of long lasting adverse reactions revealed a small number of cases most of them with either poor information or other factors not supportive of causality (e.g. 2 case reports have also systemic formulations as concomitants). In conclusion there is currently no signal from EudraVigilance on the possible link between long lasting ADRs and use of topical formulations.

However, the mentioned exacerbation of symptoms following topical use of a (fluoro)quinolone is addressed with the proposed new warning that (fluoro)quinolones should not be taken if the patient has experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone and might be reflected as part of the national communications and media campaigns.

From the healthcare professionals and academia side, a call for inclusion of nurses and pharmacist into the process was noted, echoed by general public expression of the need to increase the awareness of the risk of long-lasting, disabling and potentially irreversible ADRs associated with (fluoro)quinolones use in the whole medical community. The proposal of media/educational campaign focused not only on the newly identified risk of long-lasting, disabling or potentially irreversible ADRs but also on the (fluoro)quinolones place in the rational ATB policy is supported.

There are still many uncertainties regarding the underlying mechanism, risk factors, diagnostics and treatment options. Participants called for further scientific research stimulated by regulatory body.

More detailed information on the interventions (oral and written) is published at the EMA website.

3.2. Infectious Disease Working Party (IDWP)

The PRAC also consulted the IDWP, a WP of the Committee for Medicinal Products for Human Use, two times during the procedure.

In the first consultation, the PRAC requested the IDWP to comment on the grouping of indications from a therapeutic perspective, the changes in section 4.1 of the SmPC of the medicinal products affected and also to provide advice on the identification of the most relevant benefit data informing the review.

IDWP noted the PRAC's proposal for grouping of indications, further grouped based on benefit-risk categories. The IDWP provided comments on the relative benefit/efficacy of quinolones and fluoroquinolones for the indications placed by the PRAC into the different categories.

During the second consultation the PRAC requested the IDWP for further advice on the most appropriate wording for the indications necessitating restrictions and the proposed replacements of the too broad and medically incorrect indications from a therapeutic perspective.

The IDWP recommended that for:

- Levofloxacin and moxifloxacin, the statements supporting the restricted indications included in section 4.1 of the respective SmPCs should be kept as they were and for second-generation agents (norfloxacin, ofloxacin, lomefloxacin, pefloxacin, rufloxacin, and ciprofloxacin), the wording proposed by IDWP is as follows:

"In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections".

IDWP also provided their advice on the proposals from PRAC regarding the replacement of certain indications. It was however highlighted that the responses provided had taken into account the general properties of these antibacterial agents and that they may not necessarily apply across all approved antibacterial agents of this class since they vary in their microbiological and pharmacokinetic attributes, which in turn impact on their suitability for use in specific circumstances.

3.4. Written consultation with Healthcare Professionals and Patients

In the last stage of the review, the PRAC consulted healthcare professionals to get their views on the planned Direct Health Care Professional Communication (DHPC) and the patients on the recommended amendments to the package leaflet. The views expressed were taken into consideration by the PRAC.

3.3. Other stakeholders' interventions

The PRAC also reviewed all data submitted by different stakeholders, both before and after the public hearing. These included patients, carers, patients associations, healthcare professionals and academia. All the data submitted, via written feedback, was carefully reviewed and was reflected in the assessment as appropriate.

4. Benefit-risk assessment

(Fluoro)quinolones have been approved in the EU for a great diversity of indications - over one hundred indications of various granularities. For the purpose of this review, the indications are grouped under heading/cover terms, taking into account all available data, in particular the long-lasting, disabling and potentially irreversible adverse drug reactions.

Depending on the results of benefit/risk assessment, the indications fall in 4 categories:

- Category 1: The newly identified safety concern does not substantially modify the existing benefit/risk balance and no change in the indication is warranted.
- Category 2: The newly identified safety concern necessitates a restriction of (fluoro)quinolone use in these indications.
- Category 3: The newly identified safety concern changes benefit risk to negative and these indications shall be deleted.
- Category 4: Indications that are considered too broad in view of the evidence available and related to some (sub) indications mentioned in categories 1, 2 or 3 above. These indications shall be amended. Other indications were found to be incorrectly formulated in medical terms. They shall be removed or replaced by accurate medical terms.

Category 1: no modification of the indications

In category 1 indications, it is considered that the newly identified safety concern (long-lasting, disabling and potentially irreversible adverse drug reactions) has a limited impact on the benefit-risk balance of all (fluoro)quinolones. The benefit-risk balance remains positive and its incremental change does not warrant any amendment of the indication.

Table 11 – Category 1 indications: no modification of the indications

Indication heading
Complicated urinary tract infections/pyelonephritis
Prostatitis, epididymo-orchitis
Urethritis and cervicitis
Genital tract / gynaecological infections
Chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis
Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
Community acquired pneumonia
Pneumonia due to Gram-negative bacteria
Tuberculosis
Chronic sinusitis
Malignant external otitis
Chronic suppurative otitis media
Complicated skin and skin structure infections / Complicated skin and soft tissue infections
Gastro-intestinal infections
Bone and joint infections
Intra-abdominal infections
Prophylaxis of invasive infections due to *Neisseria meningitidis*
Inhalation anthrax (post-exposure prophylaxis and curative treatment)
Infection in immunocompromised patients

For the indications falling within this category 1, the PRAC considered that their benefit overweighs the risks, in particular the identified risk of occurrence of long lasting, disabling and potentially irreversible adverse drug reactions. This is in view of the severity of the diseases targeted, their possible serious complications including prevention of manifestations of irreversible anatomical or functional lesions, the favourable tissue distribution of fluoroquinolones and specificity of the pathogen covered by the microbiological spectrum of (fluoro)quinolones.

Therefore, PRAC concluded that these indications should be maintained.

The PRAC took the opportunity to review that the wording of the indications is in line with the current medical terminology as per antibacterial treatment guidelines (e.g. change of "prostatitis" to "bacterial prostatitis" because aetiology of prostatitis is often non-bacterial). These modifications do not affect the substance of the indications. Final recommendations on the wording of the indications falling into category 1 are displayed in the tables below for individual substances.

However, for pefloxacin PRAC considered that some of the indications mentioned should be restricted as below:

Pefloxacin

- Chronic sinusitis (CRS)

Rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and the paranasal sinuses. CRS is predominantly caused by the following pathogens: *Streptococcus*

pneumoniae, *Haemophilus influenza, Staphylococcus spp., Streptococcus pyogenes, Moraxella catarrhalis, Klebsiella pneumoniae*, anaerobes, and *Chlamydia* spp. According to Suh et Kennedy's (2012) article on Treatment options for chronic rhinosinusitis (CRS), antibiotics play a role in the management of CRS to decrease bacterial load and to treat acute bacterial exacerbations of CRS. Most experts agree that antimicrobials for treatment of CRS should provide broad-spectrum coverage.

Considering the poor pneumococcal susceptibility of pefloxacin, low activity against *S. aureus* and the safety profile of this active substance, PRAC concluded that the use of pefloxacin in the treatment of acute exacerbations of chronic sinusitis should be restricted to the patients in whom it is considered inappropriate to use other antibacterial agents for the treatment of these infections (last line option).

- Intra-abdominal infections

Fluoroquinolones, either alone or in combination with metronidazole, are recommended for the therapy of community acquired intra-abdominal infections based on the current therapeutic guidelines. Empiric antibiotic therapy for intra-abdominal infection should be driven by local microbiological results. The identified risk of occurrence of long lasting, disabling and potentially irreversible adverse drug reactions have only minor impact on the benefit/risk ratio of pefloxacin for intra-abdominal infections. However, pefloxacin has a low spectrum of activity against the indication specific pathogens. Therefore, considering insufficient coverage of the pathogens involved in this type of infection, the use of pefloxacin should be restricted to the patients in whom it is considered inappropriate to use other antibacterial agents for the treatment of these infections (last line option).

Furthermore, for pefloxacin, PRAC considered that some of the indications mentioned above in Table 11 should be removed as below:

Pefloxacin

- Acute and chronic prostatitis, including severe forms

The role of pefloxacin in the treatment of bacterial prostatitis is considered as not being demonstrated. In case of atypical sexually transmitted pathogens, such as *Mycoplasma hominis* and *Chlamydia trachomatis* or *Ureaplasma urealyticum*, pefloxacin antimicrobial activity is low (Gonzales and Henwood 1989). Apart from that, available data show a poor antimicrobial activity of pefloxacin against Pseudomonas (King and Phillips 1986) and no updated susceptibility data on pefloxacin are available as the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has not defined clinical breakpoints for pefloxacin (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Ciprofloxacin_rationale_1.9.pdf). Thus, the current role of pefloxacin for the management of bacterial prostatitis and the benefit of using pefloxacin to treat these infections is unknown. Therefore, the benefit risk-balance of this indication is considered negative for pefloxacin.

- Exacerbations of broncho-pulmonary infections in cystic fibrosis

In patients with cystic fibrosis, the predominant pathogen causing broncho-pulmonary infections is *Pseudomonas aeruginosa*. *Streptococcus* species have only moderate sensitivity to pefloxacin, with MIC90 values ranging from 3.1 to 32 mg/L (Gonzalez JP, Henwood JM. Pefloxacin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs. 1989;37(5):628-68). The poor pefloxacin antimicrobial activity against indication specific pathogen precludes its use in this indication as there is a high risk of inadequate coverage and resistance development. The current role of pefloxacin for the treatment of this indication is considered as not established. Therefore, the benefit risk balance of this indication is considered negative for pefloxacin.

- Acute uncomplicated pyelonephritis

The pathogens associated with pyelonephritis consists mainly of *E. coli* (75% to 95%), with occasional other species of *Enterobacteriaceae,* such as *P. mirabilis and K. pneumoniae,* and of *Staphylococci.* No updated data (e.g. in relation to the current prevalence of resistance in Enterobacterales and other Gram-negative bacteria) are available regarding the antimicrobial activity of pefloxacin, as no clinical breakpoints were defined by EUCAST.

Pefloxacin antimicrobial activity against bacterial strains relevant for this indication is low (Hoogkamp-Korstanje 1997). In addition, pefloxacin has low urinary excretion (34% of pefloxacin dose including its active metabolite norfloxacin) (Naber, 2001). Therefore, the benefit-risk balance in using pefloxacin in this indication is negative.

- Malignant external otitis

Malignant otitis externa (MOE), also known as necrotizing otitis externa, is a severe invasive bacterial infection that involves the external auditory canal and skull base. Almost 95% of MOE cases reported in the literature are attributed to *Pseudomonas aeruginosa* (Bovo et al. 2012, Maher 2016). As already mentioned pefloxacin has a poor antimicrobial activity against *P. aeruginosa* (Hoogkamp-Korstanje 1997), thus, the benefit is very limited. Therefore, the benefit-risk in using pefloxacin in this indication is negative.

PRAC also noted that cinoxacin, flumequine, rufloxacin are not authorised for any of the Category 1 indications and enoxacin-containing products are not authorised in the EU anymore.

The PRAC also considered that, for the medicinal products containing the following active substances, it is recommended that the wording is aligned as proposed and as relevant:

Ciprofloxacin

Current category 1 indications in product information of ciprofloxacin	**Recommended wording of category 1 indications**
Adults	
• Urethritis and cervicitis due to bacteria susceptible to fluoroquinolones	• Gonoccocal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
• Bone and joint infections	• Infections of the bones and joints
• Treatment of infections in neutropenic patients • Infection in immunocompromised patients	• Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection
Children and adolescents	
• Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*	• Broncho-pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis

Current category 1 indications in product information of ciprofloxacin	Recommended wording of category 1 indications
• Complicated urinary tract infections and pyelonephritis	• Complicated urinary tract infections and acute pyelonephritis

Levofloxacin

Current category 1 indications in product information of levofloxacin	Recommended wording of category 1 indications
• Pyelonephritis and complicated urinary tract infections (see section 4.4)	• Acute pyelonephritis and complicated urinary tract infections (see section 4.4)
• Acute exacerbation of chronic bronchitis (last line)	• Acute exacerbation of chronic obstructive pulmonary disease including bronchitis *In [indication] [name of product] 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

Current category 1 indications in product information of moxifloxacin	Recommended wording of category 1 indications
• Acute exacerbation of chronic bronchitis (last line)	• Acute exacerbation of chronic obstructive pulmonary disease including bronchitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*

Ofloxacin

Current category 1 indications in product information of ofloxacin	Recommended wording of category 1 indications

Current category 1 indications in product information of ofloxacin	Recommended wording of category 1 indications
• Pyelonephritis and complicated urinary tract infections	• Acute pyelonephritis and complicated urinary tract infections
• Prostatitis, epididymo-orchitis o Chronic bacterial prostatitis (complicated or uncomplicated) o Prostatitis by *E. coli* o Prostatitis, epididymo-orchitis o Prostatitis, infection of the epididymis and the testicle o severe prostatitis	• Bacterial prostatitis, epididymo-orchitis
• Pelvic inflammatory disease, in combination treatment o Acute pelvic inflammatory disease o Pelvic inflammatory disease, in combination treatment o Pelvic region infection in women (in combination with other antibiotics) o Inflammatory pelvic disease, in combinations treatment o Upper genital tract infection in women (see 4.4) (complicated or uncomplicated) o Upper gynaecological tract infections, including infections due to susceptible strains of *Neisseria gonorrhoeae*	• Pelvic inflammatory disease, in combination with other antibacterial agents
• Sepsis due to above-mentioned genito-urinary infections	• Urosepsis (only applicable for i.v. formulation)
• Uncomplicated cystitis (last line) o Uncomplicated cystitis o Uncomplicated cystitis (should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections) o Uncomplicated cystitis (XX should only be used if antibacterial treatment	• Uncomplicated cystitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*

Current category 1 indications in product information of ofloxacin	Recommended wording of category 1 indications
considered as first choice of treatment is deemed unfit/inappropriate)	
• Urethritis (last line) o Urethritis (should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections) o Urethritis (XX should only be used if antibacterial treatment considered as first choice of treatment is deemed unfit/inappropriate	• Urethritis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Bone and joint infections (last line) o Bone and joint infections: such as osteomyelitis or septic arthritis. (complicated or uncomplicated) o Infections of bones (osteitis, osteomyelitis) o Bone and joint infections o Gram negative infection of bones and joints o Bone infections (such as osteomyelitis and orthopaedic material/implant infection, especially when used in association with other antibiotics like rifampicin o Alternative form of treatment for bones and joints infections	• Bone and joint infections *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Severe skin and soft-tissue infections (last line)	• Complicated skin and soft-tissue infections *In [indication] [name of product] 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 sinusitis (last line)	• Acute bacterial sinusitis *In [indication] [name of product]*

Current category 1 indications in product information of ofloxacin	Recommended wording of category 1 indications
	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 bronchitis (last line)	• Acute exacerbation of chronic obstructive pulmonary disease including bronchitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Community acquired pneumonia (last line) o Community acquired pneumonia o Community acquired pneumonia (ofloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections)	• Community acquired pneumonia *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Prevention of infections due to ofloxacin susceptible pathogens (prophylaxis of infections, in patients with a significant reduction in resistance to infections (e.g., in neutropenic states)	• Prophylaxis of bacterial infection in neutropenic patients

• Non-gonococcal urethritis and cervicitis o Non-gonococcal urethritis and cervicitis o Acute non-gonococcal urethritis and cervicitis caused by *Chlamydia trachomatis* o combination therapy for the treatment of cervical infections	• Non-gonococcal urethritis and cervicitis
• Gonorrhoea	• Gonococcal urethritis and cervicitis due to susceptible Neisseria

○ Gonorrhoea ○ Gonococcal and non-gonococcal urethritis and cervicitis (complicated or uncomplicated) ○ Uncomplicated urethral and cervical gonorrhoea. ○ Uncomplicated acute gonococcal urethritis and cervicitis ○ Gonococcal urethritis due to susceptible strains of *Neisseria gonorrhoeae* and non-gonococcal urethritis	gonorrhoeae
• Chlamydia	• Non-gonococcal urethritis and cervicitis
• Tuberculosis	• Tuberculosis, in combination treatment
• Chronic sinusitis	• Acute exacerbation of chronic sinusitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Superinfection of chronic otitis (whatever its nature) and cavities after mastodectomy	• Chronic suppurative otitis media
• Bacterial gastroenteritis ○ Bacterial gastroenteritis ○ Bacterial enteritis ○ Intestinal infections ○ bacterial diarrhoea, which needs antibacterial treatment	• Infections of the gastrointestinal tract (e.g. travellers' diarrhoea) *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Abdominal and hepatobiliary infection ○ Abdominal and hepatobiliary infection ○ intra-abdominal infection ○ intra-abdominal and bile-ducts	• Complicated intra-abdmonial infections

infections ○ Infections of abdominal cavity, including pelvic area ○ Abdominal cavity infections including of the pelvic bone ○ Infections of the abdomen and the lesser pelvis • Cholangitis	
• Post-exposure prophylaxis and curative treatment of anthrax.	• Inhalation anthrax: post-exposure prophylaxis and curative treatment
• Treatment of ofloxacin sensitive prophylaxis of bacterial infections in patients with weakened resistance (for example neutropenic patients)	• Treatment of bacterial infections in neutropenic patients • Prophylaxis of bacterial infections in neutropenic patients

The MAHs should further reanalyse the current dosage recommendations, based on PK/PD considerations, for the indications, acute exacerbation of chronic sinusitis and infections of the gastrointestinal tract (e.g. travellers' diarrhoea).

Lomefloxacin

Current category 1 indications for lomefloxacin included in product information	**Recommended wording of category 1 indications**
• Acute prostatitis	• Acute bacterial prostatitis
• Acute pyelonephritis • Uncomplicated acute pyelonephritis	• Uncomplicated acute pyelonephritis

Norfloxacin

Current category 1 indications for norfloxacin included in product information	**Recommended wording of category 1 indications**
• Acute urinary tract infections in men ○ acute urinary tract infections in men ○ acute infection of lower urinary tract infections in men	• Acute urinary tract infection in men
• Uncomplicated pyelonephritis ○ uncomplicated pyelonephritis ○ acute uncomplicated pyelonephritis in	• Uncomplicated acute pyelonephritis

Current category 1 indications for norfloxacin included in product information	Recommended wording of category 1 indications
women	
• Complicated cystitis o chronic cystitis in women	• Complicated acute cystitis
• Prostatitis o prostatitis o chronic bacterial prostatitis o Acute prostatitis caused by Escherichia coli	• Bacterial prostatitis
• Gonorrhoea o gonorrhoea o uncomplicated gonorrhea o Gonococcal urethritis, pharyngitis, proctitis or cervicitis from Neisseria gonorrhoeae irrespective of the production of penicillinase. o gonococcal urethritis without signs of pelvic dissemination, in men o cervical gonorrhoea without signs of pelvic dissemination o urethral and cervical gonorrhoea o Gonorrhea (urethritis and cervicitis)	• Gonoccocal urethritis and cervicitis due to susceptible Neisseria gonorrhoeae
• Gastroenteritis o bacterial gastroenteritis o Gastroenteritis o Acute bacterial gastroenteritis o bacterial enteritis o Acute bacterial gastroenteritis after stool culture and laboratory confirmation of the susceptibility of the causative organism to NOROCIN	• Infections of the gastrointestinal tract (e.g. travellers' diarrhoea)
• Immunocompromised patients: o Infections in neutropenic patients (as	• Prophylaxis of bacterial infections in neutropenic

Current category 1 indications for norfloxacin included in product information	Recommended wording of category 1 indications
prophylaxis).	patients

The MAHs should further reanalyse the current dosage recommendations, based on PK/PD considerations, for the indication *Infections of the gastrointestinal tract (e.g. travellers' diarrhoea).*

Pefloxacin

Current category 1 indications for pefloxacin included in product information	Recommended wording of category 1 indications
• Chronic sinusitis	• Acute exacerbation of chronic bacterial sinusitis *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections*
• Gonorrhoea • Gonococcal urethritis in humans	• Gonoccocal urethritis and cervicitis due to susceptible *Neisseria gonorrhoea*
• Severe/Serious gastro-intestinal bacterial infections	• Serious gastro-intestinal bacterial infections
• Salmonella infections (carrier) • Germ carrying of salmonellosis	• Salmonella infections (carrier)
• Bone and joint infections • Bone and joint infections (gram negative osteomyelitis) • Alternative form of treatment for bone and joint infections • Infections of bone and joints (osteomyelitis caused by gram-negative microorganisms)	• Bone and joint infections

The MAHs should further reanalyse the current dosage recommendations, based on PK/PD considerations, for the indication *Serious gastro-intestinal bacterial infections.*

Prulifloxacin

Current category 1 indications for prulifloxacin included in product information	Recommended wording of category 1 indications
• Complicated infections of lower urinary tract	• Complicated urinary tract infections

For all MAs authorised based on an abbreviated dossier, the MAHs are reminded to align their product information, when relevant, with the reference medicinal product.

Category 2

For the indications falling under category 2, the risk benefit balance is considered impacted by the abovementioned safety concern in view of the benefits of (fluoro)quinolones in the concerned diseases, as well as the limited severity of some of these conditions and thus the use in these indications needs to be restricted.

Table 12 – Category 2

Indication heading
Uncomplicated cystitis • Simple uncomplicated acute cystitis • Acute cystitis in women • Simple uncomplicated acute cystitis in the premenopausal adult women • Recurrent cystitis in women • Acute uncomplicated infection of lower urinary tract (simple cystitis)
Acute exacerbation of COPD including chronic bronchitis • Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis • Acute exacerbations of chronic bronchitis • Exacerbation of chronic obstructive pulmonary disease
Acute bacterial sinusitis • Acute sinusitis • Acute bacterial sinusitis
Acute otitis media

In these indications, the affected medicinal products should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Of note, these restrictions are in addition to the restrictions that were already in place for the relevant (fluoro)quinolones at the time of the initiation of the procedure.

Uncomplicated cystitis

Based on the review of available scientific data, cases of uncomplicated cystitis have been often described as self-limiting. The recent study by Gágyor et al (*2015*) showed that two thirds of women with uncomplicated urinary tract infection treated with ibuprofen recovered without any antibiotics. However, lack of symptoms relief and risk of complications (specifically pyelonephritis) have been found to be higher in non-antibiotic group.

Reviewed European guidelines do not discuss an option of non-antibacterial therapy of urinary tract infections. According to Guidelines of the European Association of Urology (Bonkat et al 2017), antibiotic therapy should be chosen based on spectrum and susceptibility patterns of the aetiological uropathogens, tolerability, ADRs and adverse ecological effects. Nitrofurantoin, fosfomycin, trometamol or pivmecillinam are considered drugs of first choice in many countries. The guideline also states that despite lower resistance in some areas, fluoroquinolones are not considered first-line choice because of adverse effects including negative ecological effects and propensity to selection of resistance.

Inappropriate use of (fluoro)quinolones is associated with rapidly increasing bacterial resistance to these agents (*Committee on Infectious Diseases 2006*; *Murray and Baltimore 2007*). (Fluoro)quinolone resistance has appeared among commensals and uropathogens in most parts of the world, but prevalence rates vary. Recently proposed modification of fluoroquinolone breakpoints by European committee on antimicrobial susceptibility testing (*EUCAST 2016*) indicates increasing resistance to fluoroquinolones. The speed which fluoroquinolones lose their activity against invasive *E. coli* strains (isolated mostly from patients with urosepsis) is the fastest of all combinations of antibiotic-pathogen reported in EARS-NET during 2001-2015 (*ECDC 2017*).

In consideration of the current treatment guidelines, the IDWP recommendation as well as the data submitted from the MAHs, there is a consensus that uncomplicated cystitis constitutes a non-severe, non-life-threatening indication for which the potential risk outweighs the benefit when using (fluoro)quinolones as a first line treatment. During the ongoing referral procedure sufficient evidence was collected to support that (fluoro)quinolones can cause long lasting, disabling and potentially irreversible adverse drug reactions. Therefore, in section 4.1 of the SmPC, the indication uncomplicated cystitis should be reworded to be restricted to patients in whom it is considered inappropriate to use other antibacterial agents suitable for the treatment of these infections (last line option). With regard to the fact that treatment of these infections with (fluoro)quinolones is based on one dose, no exception from the restriction can be made as long lasting, disabling and potentially irreversible reactions constitute a class effect which may occur even after the first administration.

Therefore, on the basis of the benefit of using (fluoro)quinolones for the indication of uncomplicated cystitis and the known risk profile of (fluoro)quinolones the benefit-risk balance in the indication of uncomplicated cystitis is considered changed and (fluoro)quinolones should only be used in patients who have no alternative treatment options.

Acute exacerbation of chronic bronchitis (AECB) and COPD

Acute exacerbation of chronic bronchitis (AECB) is a combination of increased dyspnoea, increased sputum production, coughs and increased sputum purulence (*Wedzicha et al 2017*). The typical patient experiences 2 to 4 episodes of AECB per year (*Dever et al 2002*). More than 60% of chronic bronchitis exacerbations are caused by viral or bacterial agents (*Bandi et al 2003; Fuso et al 1995; Matkovic and Miravitlles 2013*).

Anthonisen *et al* (1987) conducted a clinical trial in 173 patients where broad-spectrum antibiotics (7 to 10 days) were evaluated over placebo. They stratified patients according to the severity of the acute

exacerbation. The occurrence of increased dyspnoea, sputum volume, and sputum purulence were defined as a Type-1 exacerbation. The occurrence of two of these symptoms were marked as Type 2, and only one of the symptoms in addition to other findings (upper respiratory infection, fever without other cause increased wheezing; increased cough; or increase in respiratory rate or heart rate by 20 % as compared with baseline) was assigned to Type 3 exacerbation. The authors showed the greatest difference in success rate between antibiotics and placebo in Type 1 (62.9 % versus 43.0 %) less in Type 2 (70.1% versus 60.0 %) and Type 3 (74.2% versus 69.7%) exacerbations. Similarly, deterioration of symptoms was decreased by antibiotic treatment in Type 1 (14.3% versus 30.5%) and Type 2 (5.2 % and 10.7 %) exacerbations and comparable deterioration of symptoms was reported in Type 3 (11.4 % and 12.1 %) exacerbations.

Nouira *et al* (2001) evaluated the efficacy of ofloxacin over placebo in COPD patients requiring mechanical ventilation. They demonstrated a significant decrease in mortality in ofloxacin group (4 % versus 22 %; absolute risk reduction 17.5 %, 95 % CI 4.3-30.7, p=0.01), in the need of additional antibiotic therapy (45.9 %, 29.1-62.7, p<0.0001), and in hospital stay (absolute difference 4.2 days, 95 % CI 2.5-5.9; and 9.6 days, 3.4-12.8, respectively).

The available meta-analysis of 16 randomised placebo-controlled clinical trials (*Vollenweider et al 2012*) showed clear benefit of antibiotic therapy in hospitalised patients with severe exacerbations. In patients with mild to moderate exacerbation the effect was not so evident. In patients with severe exacerbation, antibiotics statistically significantly reduced the risk of treatment failure (RR 0.77; 95% CI 0.65 to 0.91; I2= 47%). Mortality was statistically significantly reduced by antibiotic treatment in patients treated in the intensive care unit (ICU) (Peto OR 0.21; 95% CI 0.06 to 0.72; NNTB 6 (96% CI 3 to 24) but not in hospitalised patients in general ((Peto OR 1.02; 95%CI 0.37 to 2.79). Length of hospital stay (in days) was similar in the antibiotics and placebo groups except for the ICU study where antibiotics statistically significantly reduced length of hospital stay (mean difference -9.60 days; 95% CI -12.84 to -6.36 days). The incidence of AEs was higher in the antibiotic group (Peto OR 1.53; 95% CI 1.03 to 2.27).

European Respiratory Society in collaboration with American Thoracic Society (Wedzicha *et al* 2017) made a meta-analysis evaluating the use of antibiotics in ambulatory patients with COPD exacerbation. They realised that antibiotic therapy decreases treatment failure (27.9 % versus 42.2 %; RR 0.67, 95% CI 0.51-0.87) and prolonged the time to the next exacerbation (difference of medians 73 days, p=0.015). However, most patients in the placebo group (58%) avoided treatment failure as well. The use of antibiotics was companied by the increased occurrence of AEs (14.6 % versus 7.6 %; RR 1.84, 95 % CI 0.95-3.57) although most of them were mild. The authors concluded that the patient population should be carefully selected when deciding on antibiotic treatment. Patients with purulent sputum will likely benefit from the antibiotic treatment; the severity of the disease should also be considered. Other guidelines recommend treatment of COPD exacerbations associated with purulent sputum (NICE 2016) or fulfilling the specified criteria (GOLD 2014).

Although (fluoro)quinolones achieve high concentration in lung tissues (*Ball 1995; Boselli et al 2005; Gotfried et al 2001; Koizumi et al 1994; Soman et al 1999*), the potential existence of high bacterial loads in patients suffering from AECB is an important risk factor for the selection of resistant mutants. Moreover, in pre-existent mutation, the subsequent mutation can lead to the development of resistance to the whole group (*Davies et al 2003; Mensa and Trilla 2006*). Therefore, the local pattern of resistance, severity of exacerbation, patient´ s overall condition and possible risks associated with (fluoro)quinolones administration should be carefully considered by the health care providers (HCPs).

Taking into consideration the efficacy data, the risk of developing resistance and the risk profile of (fluoro)quinolones together with the new risk of long-lasting, disabling and potentially irreversible

ADRs it is concluded that benefit-risk balance is unchanged only in severe episodes of AECB and COPD or where other therapeutic options are not effective or tolerable. The use of (fluoro)quinolones is not warranted in mild to moderate episodes with alternative treatment options. Therefore the use of quinolones in AECB and COPD should be restricted to patients in whom it is considered inappropriate to use other antibacterial agents for the treatment of these infections (last line).

Overall, the benefit-risk balance in the indication of acute exacerbation of chronic bronchitis and COPD is considered positive only in patients who have no alternative treatment options. Furthermore, it is suggested to reword the indication "Acute exacerbations of chronic bronchitis" to "Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis".

Acute bacterial sinusitis (ABS)

ABS is generally a non-severe infection associated with high spontaneous cure rates (90%). About 80% cases of rhinosinusitis occurring in clinical practice are of viral origin and only a negligible proportion of these cases (i.e. 0,5-2%) develop to bacterial infection (*Gwaltney 1996*). It is acknowledged that it is extremely difficult to distinguish between viral and bacterial sinusitis in clinical practice (*Chow et al 2012*).

Ahovuo-Saloranta *et al* (2014) conducted a complex review assessing the treatment effect of antibiotics in treatment of an acute uncomplicated maxillary sinus infection diagnosed clinically or radiologically. This review compiled data from sixty-three (63) separate studies that used a variety of antibiotics. In clinical trials comparing antibiotic treatment versus placebo, small statistically significant effect favouring the use of antibiotics was observed in the risk of treatment failure (lack of full recovery or improvement) at 7 to 15 days (5 clinical trials, 1058 patients, RR of 0.66, 95% confidence interval (CI) 0.47 to 0.94)). The failure rates were 8.7% and 13.6% in antibiotic and placebo groups, respectively. The difference between groups in the full recovery or improvement rates was 10% at most in all the eight studies available for this comparison. The average cure or improvement rate in the antibiotic groups was 87% (range 78% to 98%) and in the placebo groups 81% (range 6 7% to 89%). Above that, complications were similar regardless of the treatment used. On the other hand, the evaluated studies indicated faster cure rate with antibiotics. However, there was not statistically significant difference at 16 to 60 day follow up (RR of 0.63, 95% CI 0.38 to 1.05) in patient without radiological sings of maxillary sinusitis (Haye *et al* 1998). Adverse effects were more common in antibiotic than in placebo groups (median of difference between groups 10.5%, range 2% to 23%).

These data are in line with the meta-analysis published by Karageorgopoulos *et al* (2008), where the authors assessed the efficacy of respiratory (fluoro)quinolones to beta-lactams in treatment of acute bacterial sinusitis.

Regarding the high success rate in placebo treated patients (Ip *et al* 2005, Ahovuo-Saloranta *et al* 2014) and the mild severity of sinusitis in majority of the cases, the benefit of antibiotics should be carefully weight against the occurrence of adverse drug reactions and the potential risk of selection of resistance.

Taking into consideration the data mentioned above and based on the risk profile of (fluoro)quinolones, including the risk of long-lasting, disabling and potentially permanent serious ADRs, (fluoro)quinolones should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of ABS infections.

Acute otitis media (AOM)

AOM is one of the most common infectious diseases in children. At present, AOM is regarded as a multifactorial and polymicrobial disease, which usually occurs as a complication of viral upper respiratory tract infection (Marom et al 2012). Respiratory viruses could be documented in the nasopharyngeal specimens of 90% of the children with AOM (Heikkinen & Chonmaitree, 2003).

Based on the available guidelines, fluoroquinolones are not routinely recommended for treatment of acute otitis media as most of the cases occur in children. In this population, the risk of cartilage toxicity associated with administration of fluoroquinolones is well-known and administration of fluoroquinolones should be initiated only after a careful benefit/risk evaluation. Based on the available data, overall 70-90% of children suffering acute otitis media reach spontaneous resolution within 7-14 days (*Rosenfeld and Kay 2003*). Nevertheless, some fluoroquinolones - especially newer ones (i.e. levofloxacin and moxifloxacin) - have been shown to be effective therapeutic option in multidrug-resistant etiological agents of acute otitis media.

Being one of the most common paediatric diseases, AOM with its spontaneous cure rate above 80% might be considered as a non-serious and in-most cases self-limited infection. According to current guidelines, amoxicillin is recommended as a first line therapy with several other treatment options for patients with hypersensitivity to penicillin.

Studies have also shown that bacterial genetic material coding for fluoroquinolone resistance can be transferred horizontally from normal oral flora, such as viridans group streptococci (*Streptococcus mitis, Streptococcus oralis*). Since frequent exposure to fluoroquinolones may allow resistance mutations to transfer from this oral flora to *S. pneumoniae* (Bell 2006), it is recommended that the use be reserved for cases where conventional antibiotics are likely to be ineffective (Leibovitz 2006; Leibovitz *et al* 2003; WHO 2008).

(Fluoro)quionolones therapy might be beneficial in patients with recurrent and/or non-responsive cases of AOM caused by the multidrug-resistant etiological agents where other conventional antibiotics are likely to be ineffective.

When the antibiotic therapy is indicated in AOM, amoxicillin is a first-line drug and there are several options for those who cannot be given oral penicillins. Children with AOM reach spontaneous resolution in many cases; therefore benefit of antibiotics in this indication is not clear. The combination of feared arthrotoxicity in children and potential bacterial resistance explosion leads to the fact that fluoroquinolones are not recommended routinely for AOM. However, since some newer fluoroquinolones (e.g. moxifloxacin, levofloxacin) are effective against multidrug-resistant etiological agents of AOM, they should be reserved for cases of recurrent/nonresponsive AOM.

In the light of newly identified risk of long-lasting, disabling or potentially permanent ADRs, the overall benefit-risk balance in the indication of otitis media (acute) has changed and should be only used in patients who have no alternative treatment option.

Category 3: deletion of indications

The indications falling within the category 3 are considered to have a benefit-risk balance negative, taking into account the abovementioned safety concern and in view of the benefits of (fluoro)quinolones in the concerned diseases.

Table 13 – Category 3 indications

Indication heading
Pharyngitis-Tonsillitis • Pharyngitis • Tonsillitis
Laryngitis
Acute bronchitis
Prophylaxis of travellers´ diarrhoea • Prophylaxis of infectious gastroenteritis (traveller's diarrhoea) • Prevention of traveller's diarrhoea
Preoperative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone
Septicaemia
Selective decontamination of gastrointestinal tract in patients with compromised immune system
Prevention of exacerbations in women with recurring urinary tract • Frequent, recurrent urinary infection prophylaxis • Long term prophylaxis of recurrent urinary infections • Prophylaxis of frequently repeating infections of urinary tract infections • Prevention of systemic urinary tract infections • Prophylaxis of systemic urinary tract infections
Prevention of infection in surgical procedures • Prophylaxis after surgeries or interventions in the urogenital system o prophylaxis after surgeries or interventions in the urogenital system o Prophylaxis of recurrent urinary infections following trans-urethral surgery or trans-rectal prostatic biopsy
Vaginal infections
Meningitis
Infection of cerebrospinal fluid
Endocarditis
Nosocomial pneumonia
External otitis

Pharyngitis-Tonsillitis

Based on the available data, approximately 90% cases of pharyngitis and 70% cases of tonsillitis in adults and children are of viral origin (Zoorob et al 2012). As for the cases of pharyngitis of bacterial aetiology, the most common pathogen causing bacterial acute pharyngitis is *Streptococcus pyogenes*.

Due to possible risks of severe post-streptococcal complications (e.g. rheumatic fever or glomerulonephritis), bacterial tonsillitis and pharyngitis should be treated by antibiotics. Treatment with several other antimicrobial agents including amoxicillin, cephalosporines (1st generation), clindamycin, clarithromycin, azithromycin, erythromycin and others has been reported to result in streptococcal eradication (Pelucchi et al 2012). Thus, there are alternative medications available in case penicillin could not be administrated and patterns of antimicrobial resistance should be always considered by HCPs.

According to evaluated data, (fluoro)quinolones reach a good target tissue concentration (Agence Française de Sécurité Sanitaire des Produits de Santé 2003; Antibiotic Steering Committee 2016; Dinis et al. 2004; Esposito et al 1990; Gotfried et al 2001; Soman et al 1999; Tapiainen et al 2016; Zoorob et al 2012). Nevertheless, (fluoro)quinolones are not sufficiently effective against relevant pathogens which are commonly presented in patients with pharyngitis and/or tonsillitis. Moreover, increasing resistance of these pathogens to fluoroquinolones and a possibility of disabling ADRs in this mostly non-severe condition needs to be considered. Therefore, fluoroquinolones are not a suitable treatment option for this indication.

The benefit-risk balance of (fluoro)quinolone use in pharyngitis and/or tonsillitis of bacterial origin is therefore considered negative.

Laryngitis

Infectious laryngitis is mostly a self-limiting viral disease (caused by parainfluenza, rhinovirus, influenza and adenovirus) that does not respond to antibiotic therapy (Higgins, 1974). The self-limiting nature of symptoms was confirmed in by Schalén et al (1985, 1993). According to available international guidelines, antibiotics should not be routinely prescribed (Agence Française de Sécurité Sanitaire des Produits de Santé 2003; Antibiotic Steering Committee 2016; Tapiainen et al 2016; Zoorob et al 2012). Taking into consideration the predominant viral aetiology of laryngitis, its mostly self-limiting nature, increasing resistance of common microorganisms to (fluoro)quinolones and the identified risk of occurrence of long lasting, disabling and potentially irreversible adverse drug reactions, the benefit/risk balance of (fluoro)quinolone use in laryngitis is considered negative.

Acute bronchitis

Generally, it is thought that most bronchial infections are of viral origin, although this has been questioned (Macfralane et al. 1994). *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catharralis* were isolated from sputum samples in up to 45% of patients with acute bronchitis (Macfarlane et al. 1993) but their role is difficult to distinguish because of potential oropharyngeal colonization in healthy individuals (Laurenzi et al. 1961; Smith and Lockwood 1986).

According to the current evidence and in line with the European guidelines (Woodhead et al. 2005, 2011), there is a modest benefit in using antibiotics for acute bronchitis in otherwise healthy individuals. As generally known, elderly frail patients and patients with comorbidities have been shown to be more sensitive to adverse effects (Moore and O'Keeffe 1999; Stahlmann and Lode 2010).

Taking into consideration the frequently viral aetiology of acute bronchitis, its mostly self-limiting nature, increasing resistance of common microorganisms to (fluoro)quinolones and the potential risk of

disabling ADRs, the benefit/risk balance of (fluoro)quinolone use in acute bronchitis is considered negative.

Prophylaxis of travellers´ diarrhoea

Most cases of travellers' diarrhoea are self-limiting and resolve spontaneously within 3-5 days. Antibiotic prophylaxis is not recommended for most travellers (CDC 2017; Hill et al 2006; Public Health Agency of Canada 2015; Riddle et al 2016). Based on the evaluation of available guidelines and position papers, the prophylaxis of travellers´ diarrhoea should be limited to high-risk short-term travellers only.

Based on the increasing resistance of pathogenic microorganisms to (fluoro)quinolones, the association of (fluoro)quinolones with *C. difficile*-associated diarrhoea, their other well-known risks in addition to the risk of rare, nevertheless persistent and disabling ADRs, the benefit/risk balance of (fluoro)quinolones in the prophylaxis of travellers´ diarrhoea is considered negative.

Preoperative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone

Chronic cholesteatomatous OM requires surgery, usually in the form of tympanomastoidectomy (tympanoplasty+mastoidectomy) in order to eradicate cholesteatoma, a usual underlying cause of chronic infection (Mittal et al. 2015). According to Verschuur et al (2004), the surgery in ears with preoperative suppuration (such as chronic otitis media with or without cholestaeatoma) is classified as clean-contaminated or dirty surgery (i.e. potentially contaminated).

The benefit of systemic antibiotic prophylaxis in general in the clean-contaminated ear surgery is currently not sufficiently substantiated and the benefit over topical antibiotics is not proven. Problems related to the use of (fluoro)quinolones in surgical prophylaxis must always be considered, including the development and dissemination of resistant pathogens and the occurrence of adverse drug reactions due to (fluoro)quinolones, including the risk of potentially disabling ADRs. Having considered the above, the PRAC considered that the benefit-risk balance of (fluoro)quinolones in preoperative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone is negative.

Septicaemia

Septicaemia is a severe and life-threatening disease associated with high mortality. Overall, septicaemia is non-specific and is generally a secondary condition (a consequence) to a primary infection. The therapy should be targeted to the primary infection taking into account PK/PD characteristics of the treatment and site of the infection. Therefore, septicaemia is not acceptable as a stand-alone indication as per the Note for Guidance (CPMP/EWP/558/95 rev 2). Thus, the indication septicaemia should be deleted.

The risk/benefit balance of (fluoro)quinolone use in septicaemia as stated is considered negative and the indication should be deleted.

Selective decontamination of gastrointestinal tract in patients with compromised immune system

Regarding the indication "Selective decontamination of gastrointestinal tract in patients with compromised immune system" the benefit of using (fluoro)quinolones is extremely limited. Indeed, the PRAC could not identify any solid evidence on the efficacy of (fluoro)quinolone use in this indication. Based on the lack of scientific evidence on efficacy and the recommendation of the IDWP, the benefit/risk balance of (fluoro)quinolone use in "Selective decontamination of gastrointestinal tract in patients with compromised immune system" is considered negative.

Prevention of exacerbations in women with recurring urinary tract infections (UTI)

Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts (Hooton 2001).

According to the European Association of Urology EAU guideline (Bonkat et al 2017), prevention of uncomplicated rUTIs includes counselling and behavioural modifications. Antimicrobial prophylaxis can be given only after counselling and behavioural modification has been attempted and when non-antimicrobial measures have been unsuccessful.

Indeed, increasing resistance to (fluoro)quinolones among uropathogens is of concern and should be taken into account when considering their place in prophylaxis of recurrent cystitis. Inappropriate use of (fluoro)quinolones is associated with rapidly increasing bacterial resistance to these agents (Committee on Infectious Diseases 2006; Murray and Baltimore 2007). (Fluoro)quinolone resistance has appeared among commensals and uropathogens in most parts of the world, but prevalence rates vary. Recently proposed modification of fluoroquinolone breakpoints by European committee on antimicrobial susceptibility testing indicates increasing resistance to fluoroquinolones. The speed with which fluoroquinolones lose their activity against invasive *E. coli* strains (isolated mostly from patients with urosepsis) is the fastest of all combinations of antibiotic-pathogen reported in EARS-NET during 2001-2015 (ECDC 2017).

Taking into consideration the risk of long-lasting, disabling and potentially irreversible ADRs that may occur even after the first administration and EAU guideline recommending avoidance of (fluoro)quinolones use both in continuous and post-coital prophylaxis due to the increasing resistance, the benefit/risk balance of (fluoro)quinolones in the indication of prevention of exacerbations in women with recurring urinary tract infection is considered negative.

Prevention of infection in surgical procedures

Boader-spectrum antibiotics should not be used for peri-procedural prophylaxis or only cautiously in very selective cases (The 2015 European Association of Urology (EAU) guidelines on Urological infections). The agent used for peri-procedural prophylaxis should ideally not be one that may be required for treatment of infections. Apart from that, same resistance patterns to pefloxacin are shared with other quinolones making pefloxacin not suitable for the use in peri-procedural prophylaxis. Considering the high resistance pattern to pefloxacin, possible development of cross resistance to other quinolones, and the newly recognised risk of long-lasting and potentially disabling adverse effects, the risks of using pefloxacin outweigh its benefits. Therefore, the risks outweigh the benefits in this indication and the indication should be deleted.

Vaginal infections (AV)

Disruption of the vaginal microbial community may occur following invasion of an exogenous organism (mono etiologic diseases such as gonorrhoea or chlamydia), or by overgrowth of one or more endogenous commensal species (bacterial vaginosis or aerobic vaginitis). The latter mechanism complicates defining the disease, identifying causative agents and distinguishing colonization from infection (Rampersaud et al 2012). Vaginal infections cover several clinical units for which the benefit of (fluoro)quinolones differs.

In Aerobic vaginitis (AV) and bacterial vaginosis (BV), the lactobacillary microflora is disturbed, with no or sporadic visible remaining lactobacillary morphotypes on microscopy specimens of vaginal fluid of affected women. AV is typically marked by either an increased inflammatory response or by prominent signs of epithelial atrophy or both (Donders et al 2015).

Group B streptococci (GBS), Escherichia coli, and Staphylococcus aureus and Enterococcus faecalis are the organisms most frequently associated with Aerobic Vaginitis (Rampersaud et al 2012). AV requires a treatment based on microscopy findings and a combined local treatment with any of the following may yield the best results: antibiotic (infectious component), steroids (inflammatory component) and/or oestrogen (atrophy component). In cases with Candida present on microscopy or culture, antifungals must be tried first, in order to see if other treatment is still needed. Vaginal rinsing with povidone iodine can provide rapid relieve of symptoms but does not provide long-term cure of the bacterial loads. Local antibiotics most suitable are preferably non-absorbed and broad spectrum, especially covering enteric gram-positive and gram-negative aerobes, like kanamycin. Latter colonisations are frequent, but inflammatory infection rare, the use of oral antibiotics in women with AV is discouraged (Donders et al 2015; Wang et al. 2016).

(Fluoro)quinolones are not recommended for the treatment of bacterial vaginosis as they do not cover indication-specific pathogens. (Fluoro)quinolones are sometimes recommended in the initial treatment of serious and/or complicated cases of aerobic vaginitis (i.e. to control acute symptoms in severe cases such as staphylococcal or macular streptococcal vaginitis). Based on the efficacy data, current treatment guideline, known risk profile of (fluoro)quinolones including the newly identified disabling ADRs and in line with IDWP recommendation (that the benefit of using (fluoro)quinolones in vaginal infections is extremely limited), the PRAC considered that benefit-risk balance of (fluoro)quinolones in vaginitis is negative.

Meningitis

In EU, the indication of meningitis is only authorised for pefloxacin.

(Fluoro)quinolones have not been extensively studied for the treatment of acute bacterial meningitis and therefore there is only sparse data available regarding the use of pefloxacin in patients with meningitis that do not allow establishing efficacy.

Considering potential insufficient coverage of pathogens responsible for meningitis by pefloxacin and risks associated with inappropriate treatment of meningitis, the overall benefit/risk balance of this indication is considered negative and therefore should be deleted.

Infection of cerebrospinal fluid

There is no avalaible data establishing efficacy in this clinical setting. Furthermore, the terminology '*Infection of cerebrospinal fluid'* is considered by the PRAC to be incorrect from a medical perspective. The benefit-risk balance is therefore negative and the indication should be deleted.

Endocarditis

In the EU, the indication endocarditis is approved exclusively for pefloxacin.

Infective endocarditis is a severe and life-threatening disease associated with high mortality. Typical microorganisms that can cause infective endocarditis include Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus or enterococci.

After review of the available data, mainly based on animal models (Giamarellou H et al. 1989), efficacy of pefloxacin cannot be established.

Considering potential insufficient coverage of pathogens responsible for endocarditis by pefloxacin and risks associated with inappropriate treatment of endocarditis, the overall benefit/risk balance of this indication is considered negative.

Nosocomial pneumonia

The poor antimicrobial activity of pefloxacin to *Pseudomonas aeruginosa* precludes from its use in nosocomial pneumonia where *P. aeruginosa* is a frequent pathogen. Furthermore, activity of ofloxacin against relevant pathogens is too limited to justify use in nosocomial pneumonia. In these infections complicated course as well as high level of the resistant pathogens should be expected. The overall benefit/risk ratio for this indication for is therefore considered negative.

External otitis

Acute otitis externa is a cellulitis of the ear canal skin and sub-dermis, with acute inflammation and variable oedema. In majority of cases, otitis externa is caused by bacterial infection (Dibb 1991; Rosenfeld et al. 2014), however, also other causative agents such as fungal infection or non-infectious dermatologic processes should be considered. In case of bacterial otitis externa, the main common causative pathogens are *Pseudomonas aeruginosa* and *Staphylococcus aureus*, often occurring as a polymicrobial infection (Dibb 1991; Clark et al. 1997). While the efficacy of topical antibacterial therapy was confirmed in clinical trials, the use of systemic therapy is questionable (Freedman 1978; Yelland 1993; Cannon 1970) and should be limited to persistent otitis externa or local or systemic spread of the infection (Sander 2001).

In view of the above, the overall benefit-risk balance for this indication is therefore considered negative.

Category 4: rewording of indications according to the current medical knowledge

Indications in this category are amended as they are either:

(1) too broad and encompass too many medical entities in terms of the scientific evidence available for (fluoro)quinolone benefit/risk assessment, in view of the *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)* and in relation to the (sub) indications mentioned in categories 1, 2 or 3 above. Therefore these broad indications need to be amended.

(2) Or the terminologically is incorrect from a medical perspective.

Table 14 – Category 4 indications that are too broad

Indication heading
Infections of kidney, urinary tract and genitals
Urinary tract infection
Respiratory infections
Pneumonia
Ear, nose and throat infections
Skin and soft tissue infections
Genital tract infections
Gyneacological infections

Table 15 – Category 4 indications that are incorrectly formulated

Indication
Infection of the digestive system and bile ducts

Prevention of infection in surgical procedures
Prophylaxis of systemic urinary tract infections
Prevention of systemic urinary tract infections

Ciprofloxacin

Current indication for ciprofloxacin	Indications to be amended in line with the wording below
○ Urinary tract infection	• Uncomplicated acute cystitis *In [indication] [name of product] 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 pyelonephritis • Complicated urinary tract infections

Levofloxacin

Current indications for levofloxacin	Indications to be amended in line with the wording below
• skin and soft tissue infections • skin and soft structure infections	Complicated skin and soft tissue infections / Complicated skin and skin structure infections *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*

Ofloxacin

Current indications for ofloxacin	Indications to be amended in line with the wording below
• Urinary tract infections ○ Urinary tract infection ○ Upper and lower urinary tract infections ○ Upper and lower urinary tract infections, complicated or not ○ Infections of the upper and lower urinary tract ○ Upper and lower, acute and chronic urinary tract infections ○ Complicated and uncomplicated urinary tract infections (cystitis and pyelonephritis) ○ Upper and lower urinary tract infections coming from bacteria such as E. coli, K. pneumoniae, Proteus, P. aeruginosa	• Uncomplicated acute cystitis *In [indication] [name of product] 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 pyelonephritis • Complicated urinary tract infections

Current indications for ofloxacin	Indications to be amended in line with the wording below
• Lower urinary tract infections ○ Acute and chronic lower urinary tract infections	• Uncomplicated acute cystitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Complicated urinary tract infections
• Sinusitis ○ Sinusitis	• Acute bacterial sinusitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Chronic bacterial sinusitis
• Respiratory infections ○ Acute, chronic or recurrent respiratory tract infections; superior – acute otitis media, otitis externa, sinusitis, pharyngitis and laryngitis ○ Acute, chronic or recurrent respiratory tract infections caused by Haemophilus influenzae or other Gram-negative or multi-resistant pathogens, as well as by Staphylococcus aureus ○ Respiratory tract infections (with the exception, if infection is of pneumococcal origin or is suspected) ○ Severe respiratory infections caused by gram-negative bacilli and susceptible staphylococci ○ Lower respiratory tract infections	• Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Community-acquired pneumonia *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Pulmonary infections ○ Pulmonary infections [such as: acute exacerbation of chronic bronchitis, exacerbation of cystic fibrosis, nosocomial pneumonia, pulmonary tuberculosis by resistant mycobacteria, especially in immunocompromised patients (minor anti-tuberculosis medicine)]	• Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Community-acquired pneumonia *In [indication] [name of product] should be used only when it is considered inappropriate to use*

Current indications for ofloxacin	Indications to be amended in line with the wording below
	other antibacterial agents that are commonly recommended for the treatment of these infections. • Pulmonary tuberculosis by resistant mycobacteria, especially in immunocompromised patients (minor anti-tuberculosis medicine)
• Pneumonia o Pneumonia, especially when caused by so-called "problematic" germs such as: E. coli, Klebsiella, Enterobacter, Proteus, Pseudomonas, Legionella or Staphylococcus o Pneumonia, above all if it's caused by bacteria such as Escherichia coli, Klebsiella, Enterobacter, Proteus, Pseudomonas, Legionella or Staphylococcus	Community-acquired pneumonia. *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Bronchial suppurations, in the absence of any parenchymal lesion ▪ In chronic bronchitis during recurrent exacerbations • Bronchial suppurations, in the absence of any parenchymal lesion: ▪ In subjects at risk (chronic alcoholism, smoking, subjects over 65 years)	Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*
• Ear, nose and throat infections o Ear, nose and throat infections (with the exception of acute tonsillitis)	• Acute bacterial sinusitis *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Chronic bacterial sinusitis • Acute otitis media *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Chronic suppurative otitis media
• Chronic ear, nose and throat infections o Severe chronic ENT infections caused by gram-negative bacilli and	• Chronic bacterial sinusitis • Chronic suppurative otitis media

Current indications for ofloxacin	Indications to be amended in line with the wording below
susceptible staphylococci ○ Chronic and recurrent infections of the nose, throat and ear, only when caused by Gram-negative pathogens, including Pseudomonas, or by Staphylococci ○ Chronic and recurrent infections of ears, nose and throat, above all if they are caused by gram-negative bacteria including Pseudomonas, or if they are caused by Staphylococcus ○ Ear, nose and throat (ENT) infections (such as: chronic sinusitis, superinfection in chronic otitis, prophylaxis of infections following inner ear surgery) ○ Chronic and recurrent otorhinolaryngological infections	
• Genital tract infections ○ Infections of genital organs ○ Infections of genitals ○ Severe genital tract infections caused by gram-negative bacilli and susceptible staphylococci	• Bacterial prostatitis, epididymo-orchitis including cases due to susceptible Neisseria gonorrhoeae • Urethritis and cervicitis including cases due to susceptible Neisseria gonorrhoeae
• Gynaecological infections ○ Gynaecological infections	• Urethritis and cervicitis including cases due to susceptible Neisseria gonorrhoeae • Pelvic inflammatory disease including cases due to susceptible Neisseria gonorrhoeae
• Skin and soft tissue infections ○ Skin and soft tissue infections ○ Gram negative infection of skin and soft tissue ○ Skin and soft tissues infections or infections of traumas from microbes such as E. coli, K. pneumoniae, Enterobacter, P. mirabilis and P. vulgaris, Providencia, Citrobacter, P. aeruginosa, S. aureus	• Complicated skin and soft tissue infections *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.*

Lomefloxacin

Current indications for lomefloxacin	Indications to be amended in line with the wording below
Urinary tract infections	• Simple uncomplicated cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections* • Acute uncomplicated pyelonephritis
Lower respiratory tract infections	• Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.*

Norfloxacin

Current indications for norfloxacin	Indications to be amended in line with the wording below
• Cystitis ○ Cystitis ○ Acute and chronic cystitis in women	• Uncomplicated acute cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Complicated acute cystitis
• Lower urinary tract infections ○ Lower urinary tract infections	• Uncomplicated acute cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Urethritis including cases due to susceptible Neisseria gonorrhoeae

	• Complicated acute cystitis
• Urinary tract infections ○ Urinary tract infections ○ Complicated and uncomplicated upper and lower urinary tract infections: cystitis, pyelitis, cystopyelitis ○ Upper and lower urinary tract infections, including cystitis, pyelitis and cystopyelitis caused by norfloxacin susceptible bacteria ○ Complicated and uncomplicated urinary tract infections ○ Acute urinary tract infections in men ○ Other lower urinary tract infections, including prostatic infections, and upper urinary tract infections with susceptible bacteria, in adults (i.e. other than uncomplicated acute cystitis) ○ Acute (except acute pyelonephritis) and chronic (except chronic complicated pyelonephritis) infections of urinary tract caused by sensitive microorganisms ○ Acute and chronic urinary tract infections, uncomplicated (cystitis, pyelitis) and complicated, excluding complicated pyelonephritis, acute or chronic ○ Acute infection of lower urinary tract infections in men ○ Acute lower urinary tract infection in men	• Uncomplicated acute cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Urethritis including cases due to susceptible Neisseria gonorrhoeae • Complicated urinary tract infections (except complicated pyelonephritis) • Complicated acute cystitis
• *Urinary tract and related infections* ○ *Complicated and uncomplicated, acute and chronic, upper and lower urinary tract infections. These infections include: cystitis, pyelitis, chronic prostatitis and infections related to urological surgical procedures, neurogenic bladder or nephrolithiasis (except acute and chronic complicated pyelonephritis) caused by bacteria sensitive to norfloxacin* ○ *Upper and lower, complicated and uncomplicated, acute and chronic urinary tract infections. These infections include cystitis, pyelitis, chronic prostatitis and those*	• Uncomplicated acute cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.* • Bacterial prostatitis • Epididymo-orchitis including cases due to susceptible Neisseria gonorrhoeae • Urethritis including cases due to susceptible Neisseria gonorrhoeae • Complicated urinary tract infections (except complicated pyelonephritis) • Complicated acute cystitis

urinary infections associated with urological surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to [name of product] ○ *Upper and lower, complicated and uncomplicated, acute and chronic urinary tract infections. These infections include cystitis, pyelitis, pyelocystitis, pyelonephritis, chronic prostatitis, epididymitis and those urinary tract infections associated with urological surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to [name of product]*	
Medically incorrect indications	
• Prophylaxis of systemic urinary tract infections • Prevention of systemic urinary tract infections	• Perioperative prophylaxis in invasive urological surgery

Pefloxacin

Current indications for pefloxacin	**Indications to be amended in line with the wording below**
• Respiratory tract infections ○ Respiratory infections ○ Respiratory infection - severe infections caused by gram-negative bacilli and susceptible staphylococci ○ Infection of respiratory tract (acute exacerbation of chronic bronchitis, exacerbation in cystic fibrosis, nosocomial pneumonia)	• Acute bacterial sinusitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections* • Acute exacerbation of chronic bacterial sinusitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.* • Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.*
• Pulmonary infections ○ Pulmonary infections (acute	• Acute exacerbations of chronic obstructive pulmonary disease including chronic

Current indications for pefloxacin	Indications to be amended in line with the wording below
exacerbation of chronic bronchitis, exacerbation of cystic fibrosis, nosocomial pneumonia)	bronchitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.*
• Ear, nose and throat infections o Ear, nose and throat infections o Ear, nose and throat infection - severe infections caused by gram-negative bacilli and susceptible staphylococci o Ear, nose and throat (ENT) infections (such as: chronic sinusitis, external otitis) o Ear nose and throat infections (such as chronic sinusitis, malignant otitis externa)	• Acute bacterial sinusitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.* • Acute exacerbation of chronic bacterial sinusitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.*
• Urinary infections o Urinary tract infections o Urinary infection - severe infections caused by gram-negative bacilli and susceptible staphylococci o Urinary tract infections (including prostatitis) o Infections of urinary tract (inclusive of prostatitis) o Urinary tract infections (acute or recurrent cystitis, acute uncomplicated pyelonephritis)	• Acute uncomplicated cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections*
• Genital tract infections o Genital infections (chronic prostatitis) o Genital tract infection - severe infections caused by gram-negative bacilli and susceptible staphylococci	• Gonococcal urethritis and cervicitis including cases due to susceptible Neisseria gonorrhoeae
• Abdominal and hepato-biliary infections o Abdominal infections o Abdominal infections - severe infections caused by gram-negative bacilli and susceptible staphylococci o Hepatobiliary infections o Hepatobiliary infection - severe infections caused by gram-negative bacilli and susceptible staphylococci	• Hepato-biliary infections • Complicated intra-abdominal infections. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections*

Current indications for pefloxacin	Indications to be amended in line with the wording below
○ Infections of bile ducts	
• Skin and soft tissue infections ○ Skin infections ○ Skin infection - severe infections caused by gram-negative bacilli and susceptible staphylococci ○ Skin and soft tissue infections by penicillin resistant Staphylococcus ○ Infections of skin and soft tissue caused by staphylococcus resistant to penicillin	• *Complicated skin and soft tissue infections. In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections*

Rufloxacin

Current indications for rufloxacin	Indications to be amended in line with the wording below
Lower respiratory tract infections	• Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections*
Urinary tract infections	• Uncomplicated acute cystitis. *In [indication] [name of product] should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections*

Overall conclusions

(Fluoro)quinolones are an important class of antibiotics with a broad spectrum of activity against many different bacterial strains. According to current evidence and recommendations they should not be prescribed as first-line antibacterial agents, except for certain serious conditions and in specific situations (e.g. where oral administration is clearly advantageous and/or sensitivity of the causative microorganisms have been ascertained). The risk of emerging bacterial resistance to (fluoro)quinolones should be decreased by not overusing them and reserving their use only to most severe conditions.

Generally, the safety profile of (fluoro)quinolones has been well characterized . Most of the adverse effects are mild and frequent, others are rare but severe; gastrointestinal (nausea, vomiting, diarrhoea

etc.) and central nervous system (dizziness, insomnia, confusion, headache etc.) reactions are the most common. Some rare but serious adverse reactions have been detected, described and listed in product information of different (fluoro)quinolones. These are mainly tendon, muscle and joint disorders, neurologic and psychiatric disorders.

The PRAC has concluded that some of the serious adverse reactions could very rarely be long-lasting, disabling and potentially irreversible.

It is considered that this specific risk is a class effect of all (fluoro)quinolones because similar biochemical mechanisms seem to underlie these ADRs. For some (fluoro)quinolones agents, no long-lasting, disabling and potentially irreversible adverse reactions have been reported so far. However, it is reasonable to assume that these ADRs could be caused by any agent of the (fluoro)quinolones group and would be detected if exposure is sufficiently extensive.

Although incidence of these reactions seems to be low taking into account to the high consumption of (fluoro)quinolones across the EU, their severity must be taken into consideration when evaluating benefits and risks of (fluoro)quinolone use in clinical practice.

For patients suffering from a serious infection caused by a microorganism that is susceptible to these antibiotics, fluoroquinolones remain an important treatment option despite the overall risk related to the use of these medicinal products including the risk of the long-lasting, disabling and potentially irreversible adverse reactions.

However, in case of milder infections, benefit and risk should be carefully weighed and other treatment options should always be considered. In such cases, fluoroquinolones should be reserved as a last line treatment in patients where other therapeutic options are not effective or are not tolerated.

In mild and/or self-limiting infections, the modest benefit of (fluoro)quinolones treatment does not outweigh the overall risk related to the use of these medicinal products including the risk of long-lasting, disabling and potentially irreversible adverse reactions as other treatment without such risk could be used, or antibiotic treatment is not necessary at all.

These restrictions, both in the line of treatment as well as deletion of certain indications where the benefit-risk balance is negative, are a key measure in order to ensure the appropriate use of (fluoro)quinolones.

Significant amendments of the product information of fluoroquinolone-containing medicinal products are proposed to reflect these conclusions.

Benefit risk balance of four substances (pipemidic acid, nalidixic acid, flumequine and cinoxacin) is considered negative. The MAH should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of these medicinal products in any indication. For doing so, the MAHs should justify the dosage recommendation and consider generate PK/PD data in support. Due to their chemical structure and the related pharmacodynamic and pharmacokinetic profile (very narrow range of anti-bacterial activity, high minimal inhibitory concentrations) their benefit is limited based on the current available data. It is also noted that these substances are not mentioned in any clinical guidelines and their place in the therapeutic armamentarium of urinary / genital / gastro-intestinal infections is not justified anymore. Considering the limited benefit and in view of the overall risk related to the use of these medicinal products including the risk of long-lasting, disabling and potentially irreversible reactions, the benefit-risk balance of these medicinal products is negative.

5. Risk management

5.1. Pharmacovigilance activity

6.1.1. Detailed follow-up of selected spontaneous reports and PSUR monitoring

All MAHs are required to perform a detailed follow-up of all incoming spontaneously reported cases of prolonged, potentially irreversible, serious suspected adverse drug reactions to fluoroquinolones. Reactions that have lasted more than 30 days are of special concern as well as reactions that result in a substantial disruption of a person's ability to conduct normal life functions. The follow-up should focus on (but should not be limited to) the information about patient´s age and sex, fluoroquinolone medication (substance, route of administration, indication, start date, date of last dose), adverse drug reaction (start, duration, intensity over time, affection of everyday life activities) and risk factors (previous physical activity, renal impairment, recent/concomitant use of statins or corticosteroids, solid organ transplantation). In terms of electronic transmission of relevant ICSRs, the following data fields should always be attended if sufficient information is available:

Seriousness criterion E.i.3.2d Disabling / Incapacitating

E.i.6 Duration of Reaction / Event

E.i.7 Outcome of Reaction / Event at the Time of Last Observation

A cumulative review of all these cases of long-lasting, disabling and potentially irreversible ADRs with a particular focus on risk factors should be performed in 5 years by the MAHs and should be submitted as part of the PSURs for MAHs required submitting a PSUR *as per* EURD list.

The PSUR submission dates for fluoroquinolones should be harmonised through the EURD list in view of the above cumulative review.

5.1.1. Non- interventional studies

Drug utilisation study

As outcome of the referral procedure, restriction of indications, other changes of the product information and a DHPC are being recommended (see section 6.2 below). The implementation of these risk minimisation measures is intending to avoid unnecessary and inappropriate use of fluoroquinolone, in particular in view of the risk of long-lasting, persistent and potentially irreversible adverse drug reaction.

As such the PRAC considers that the effectiveness of the newly introduced risk minimisation measures should be monitored and evaluated by the means of a drug utilisation study (DUS) conducted in order to investigate changes in prescribing behaviour in the outpatient setting. This study should take into account data available from the European Centre for Disease Prevention and Control (ECDC) and should be representative of a broad range of Member States.

Taking into account the PRAC criteria for impact research, as well as the very high number of products and MAHs concerned, and in order to obtain meaningful and reliable results regarding the effectiveness of the risk minimisation measures recommended, the PRAC considers that the regulatory actions proposed for quinolones and fluoroquinolones medicinal products would benefit from the conduct of an

independent EMA-funded study in accordance with the principles laid down in the PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1) (EMA/165407/2017).

5.2. Risk minimisation activities

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information are necessary in order to reflect and minimise the risk of long-lasting, disabling and potentially irreversible adverse drug reactions associated with the use of quinolone- and fluoroquinolone-containing medicinal products. Further warnings and precautions of use relating to the long-lasting, disabling and potentially irreversible adverse drug reactions associated with the use of quinolone- and fluoroquinolone-containing medicinal products were also included and other important information harmonised.

These changes include amendments to sections 4.1, 4.4 and 4.8 of the SmPC.

The Package Leaflet was amended accordingly.

5.2.2. Direct Healthcare Professional Communications/Communication plan

A DHPC is proposed to be sent to the health care professionals, to increase the awareness on the risk of long-term, persistent, potentially irreversible ADRs and the associated changes to the product information.

The following specialties are recommended to be targeted: general practitioners, otorhinolaryngologists, specialists in internal medicine, pulmonologists, urologists, gynaecologists, intensive care physicians, surgeons, dermatologists, ophthalmologists, neurologists, orthopaedists, dentists especially periodontists, infectious disease specialists.

The NCAs should decide which specialties are relevant to receive the DHPC based on the national clinical practice. NCAs should also decide whether any other specialty should be added to the above stated list.

6.2.4. Media campaign

PRAC also concluded that further communication of the outcome of this review to relevant health care providers and health organisations, including media campaigns if appropriate could be considered by NCAs.

6. Condition for lifting the suspension

For the suspension to be lifted for nalidixic acid, flumequine, pipemidic acid and cinoxacin, the Marketing Authorisation Holder shall provide the following:

- The MAH should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.

7. Grounds for Recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for medicinal products containing substances related to quinolones and fluoroquinolones for systemic and inhaled use.
- The PRAC considered the totality of the data submitted for quinolones and fluoroquinolones medicinal products with regard to long-lasting, disabling and potentially irreversible ADRs. This included the responses submitted by the marketing authorisation holders in writing as well as the outcomes of consultations with the Infectious Disease Working Party. In addition, the PRAC considered the views of patient organisations, patients, families and carers, and the views of healthcare professionals in a public hearing. The PRAC also reviewed all data submitted by different stakeholders, both before and after, the public hearing.
- The PRAC concluded that some of the serious adverse drug reactions associated with the use of quinolones and fluoroquinolones could very rarely be long-lasting, disabling and potentially irreversible and that these risks are a class effect.
- The PRAC concluded that for patients with a serious infection that is susceptible to these antibiotics fluoroquinolones remain an important treatment option despite the very rare risk of long-lasting, disabling and potentially irreversible adverse reactions.
- The PRAC concluded that in case of milder infections, other treatment options should be considered. Therefore fluoroquinolones should be reserved as a last line treatment in patients where other therapeutic options are not effective or not tolerated.
- The PRAC also concluded that in case of mild and/or self-limiting infections, the benefit of quinolones and fluoroquinolones treatment does not outweigh the overall risk related to the use of these medicinal products including serious risk of long-lasting, disabling and potentially irreversible adverse drug reactions.
- As a consequence, the PRAC recommended the suspension of the following quinolones medicinal products, nalidixic acid, pipemidic acid, cinoxacin and flumequine, as they do not retain any indication with a positive benefit-risk. To lift the suspension the MAH should submit the appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product.
- Also, the PRAC recommended changes to the product information including the indication and further warnings and precautions of use relating to the long-lasting, disabling and potentially irreversible adverse drug reactions.
- Core elements of a direct healthcare professional communication were agreed, together with the timelines for its distribution.

In view of the above, the Committee considers that the benefit-risk balance of the following fluoroquinolone medicinal products, pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin remains favourable subject to the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin.

The Committee also considers that the benefit-risk balance of the following quinolone medicinal products, nalidixic acid, pipemidic acid, cinoxacin and flumequine is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisations nalidixic acid, pipemidic acid, cinoxacin and flumequine.

The condition imposed to lift the suspension of the marketing authorisation is set out in section 6 of this report.

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