Annex II

Scientific conclusions

Scientific conclusions

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.

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

While these ADRs are already 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.

The PRAC adopted a recommendation on 16 October 2018 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The PRAC considered the totality of the data submitted for (fluoro)quinolones 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.

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.

Risk factors associated with appearance of the assessed ADRs remain one of the main uncertainties and further examination of the risk factors should be further explored. Relevant stakeholders, including academia and MAHs, are encouraged to perform further research that would further characterise 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, treatments for the ADRs, identification of possible biomarkers to predict these ADRs and underlying mechanisms of action that could lead to the respective reactions.

(Fluoro)quinolones have been approved in the EU for a 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 impact of the long-lasting, disabling and potentially irreversible adverse drug reactions on the benefit-risk balance of these indications:

- Category 1: The newly identified nature of the safety concerns does not substantially modify the existing benefit/risk balance and no change to 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: The Indications 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 quinolones/ fluoroquinolones containing products. The benefit-risk balance remains positive and its incremental change does not warrant any amendment to the indication.

Table 1 – 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 (fluoro)quinolones and specificity of the pathogen covered by the microbiological spectrum of (fluoro)quinolones.

Therefore, PRAC concluded that these indications should be maintained.

However, for pefloxacin PRAC considered that some of the indications mentioned above in Table 1 should be restricted as below:

- Chronic sinusitis (CRS)

  Rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and the paranasal sinuses. Mainly CRS is caused by the following pathogens: *Streptococcus pneumoniae*, *Haemophilus influenza, Staphylococcus spp., Streptococcus pyogenes, Moraxella catarrhalis, Klebsiella pneumoniae*, anaerobes, and *Chlamydia* spp. Considering the poor pneumococcal susceptibility of pefloxacine and the potential risks, 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

  Considering insufficient coverage of the pathogens involved in these infections, PRAC conclude that 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 1 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, the available data shows 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). It should be noted that pefloxacin has a poor antimicrobial activity against *P. aeruginosa*, thus, the benefit is very limited. Therefore, the benefit-risk in using pefloxacin in this indication is negative.

Category 2: indications to be restricted

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 2 – Category 2 indications

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

For these indications, the (fluoro)quinolones 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.

The recommendation for the restriction to last line is based on the below:

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. Inappropriate use of (fluoro)quinolones is associated with rapidly increasing bacterial resistance to these agents (*Committee on Infectious Diseases 2006*; *Murray and Baltimore 2007*).

It is considered that uncomplicated cystitis constitutes a non-severe, non-life-threatening indication for which the potential risk outweighs the benefit when using (fluoro)quinolones as first line treatment. Therefore, 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

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.

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.

Acute bacterial rhinosinusitis (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*).

Regarding the high success rate in placebo treated patients 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.

Therefore in view of the risk related to the use 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 regarded as a multifactorial and polymicrobial disease, which usually occurs as a complication of viral upper respiratory tract infection (Marom et al 2012). 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. (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.

Therefore in view of the risk related to the use of (fluoro)quinolones, including the 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 limited benefits of (fluoro)quinolones in the concerned diseases.

Table 3 – 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

Indication heading
Vaginal infections
Meningitis
Infection of cerebrospinal fluid
Endocarditis
Nosocomial pneumonia
External otitis

For these indications, the recommendation for the deletion of the indication is based on the below:

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.*

(Fluoro)quinolones do not sufficiently cover the spectrum of pathogens which are commonly identified in patients with pharyngitis and/or tonsillitis. Moreover, increasing resistance to (fluoro)quinolones and a possibility of disabling ADRs in this mostly non-severe condition needs to be considered. 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). 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, the most bronchial infections are of viral origin. *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.

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

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. Taking into consideration the risk of long-lasting, disabling and potentially irreversible ADRs 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)

Group B *streptococci* (GBS), *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis* are the organisms most frequently associated with Aerobic Vagnitis (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 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 risks related to the use of (fluoro)quinolones including disabling ADRs 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 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 benefit-risk balance for this indication is considered negative.

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

Indications in this category are amended (please refer to Annex III) 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 terminology is incorrect from a medical perspective.

Table 4 – Category 4 indications that are considered 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 5 – Category 4 indications to be reworded according to accurate medical terms

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

Details of the amendments/ rewording of category 4 indications mentioned in tables 4 and 5 above are provided in Annex III of the CHMP opinion.

In addition to the amendments to the indications mentioned above, the PRAC recommended other changes to the product information including further warnings and precautions of use relating to the long-lasting, disabling and potentially irreversible adverse drug reactions.

The PRAC also recommended the suspension of the following quinolones medicinal products, nalidixic acid, pipemidic acid, cinoxacin and flumequine. The benefit risk balance of four substances (pipemidic acid, nalidixic acid, flumequine and cinoxacin) is considered negative. Indeed, 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. To lift the suspension, the MAH should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of these medicinal products. The MAHs should justify the dosage recommendation and consider appropriate PK/PD data in support of the indication.

Core elements of a direct healthcare professional communication were agreed, together with the timelines for its distribution.

Grounds for PRAC 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 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 PRAC concluded 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 PRAC also concluded that the benefit-risk balance of the following quinolone medicinal products, nalidixic acid, pipemidic acid, cinoxacin and flumequine is no longer favourable and should be suspended. For lifting the suspension, the PRAC recommended that the MAH should submit the appropriate scientific evidence to demonstrate a positive benefit-risk of the medicinal product in any indication.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.