Medicines & Healthcare products Regulatory Agency

Review of risk minimisation for disabling and potentially long-lasting/irreversible side effects associated with fluoroquinolone antibiotics

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

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Contents

1. Plain Language Summary

Key messages:

Fluoroquinolones are a class of antibiotics that include ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, and ofloxacin – these medicines may also have a brand name so patients should check the details of all antibiotics prescribed to them.

Fluoroquinolone antibiotics can cause serious side effects which may affect multiple parts of the body, potentially including tendons, muscles, joints, nerves, or mental health – in some patients, these side effects have caused long-lasting or permanent disability.

To reduce the risk of these side effects, healthcare professionals must now only prescribe fluoroquinolone antibiotics in situations when other antibiotics, that are commonly recommended for the infection, are inappropriate.

Stop taking your fluoroquinolone antibiotic and contact your doctor immediately if you have any of the following signs of a side effect:

- tendon pain or swelling – if this happens, rest the painful area until you can see your doctor
- pain in your joints or swelling in joints such as in the shoulders, arms, or legs
- abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in the legs or arms, or difficulty walking
- severe tiredness, depressed mood, anxiety, problems with your memory or severe problems sleeping
- changes in your vision, taste, smell or hearing

Tell your doctor if you have had any of the above effects at any point while taking a fluoroquinolone – this means you should avoid them in the future.

Introduction

Fluoroquinolone antibiotics given by mouth, injection, or inhalation are associated with a risk of serious, disabling, long-lasting and potentially irreversible side effects. The frequency of these drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the rare frequency category). These side effects may affect multiple body systems particularly the musculoskeletal and nervous system. They have been reported in patients irrespective of their age and potential risk factors.

Restrictions to the use of fluoroquinolones were introduced in 2019 after the outcome of a European review to minimise the risk of these side effects. These new measures restricted the use of antibiotics for specific mild to moderate infections.

Since the conclusion of the European review and implementation of these restrictions in the UK, the MHRA has continued to receive reports of disabling and potentially long-lasting or irreversible side effects in association with fluoroquinolones. Additional evidence has also become available since the 2019 review from a study looking at the prescribing of fluoroquinolones in 6 European countries, including the UK (Ly NF et al.). As a result of these factors, MHRA decided to undertake another UK-based review, to look at the effectiveness of measures in place to reduce the risk of side effects.

A Drug Safety Update was released in August 2023 to remind healthcare professionals of these risks and to advise that the MHRA is conducting a further review and will communicate any additional regulatory action in due course. At this time, a letter was also sent to healthcare professionals to remind them of the risks.

More information about this medicine

Fluoroquinolones are a class of antibiotic; they are used to treat infection. They are used as a treatment option in a number of different types of infection, including respiratory tract infections, ear, nose and throat infections, skin and soft tissue infections, and genital and urinary tract infections.

Fluoroquinolone antibiotics include ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, and ofloxacin – these medicines may also have a brand name so patients should check the details of all antibiotics prescribed to them.

Fluoroquinolones are used in both primary care (for example by GPs) and secondary care (for example prescribed in a hospital).

Information considered in the latest review

The MHRA presented the data and evidence to the Commission on Human Medicines (CHM) who were asked to provide independent advice and recommendations.

The CHM considered information summarised by the MHRA on risks linked to fluoroquinolones, including data from the results of a European Drug Utilisation Study (DUS) of prescribing trends following the European review, UK Yellow Card data (voluntary reporting of side effects from healthcare professionals and the public), data from publications investigating disability and serious side effects in association with fluoroquinolones, and information from the lived experience of patients (including 53 written responses). The CHM also heard directly from patients and patient representatives about

their experiences of side effects associated with fluoroquinolones. Data were also presented to the CHM about the numbers of patients in the UK in primary care taking fluoroquinolone antibiotics and how this has changed over the years. In coming to its advice, the CHM heard from experts on how fluoroquinolones are being used and how the existing regulatory measures have impacted on the use of fluoroquinolones.

Advice from CHM

The CHM carefully considered the data and evidence and measures for reducing the risks associated with fluoroquinolones.

The CHM noted that there are multiple factors that will contribute to reducing the risks associated with fluoroquinolones, and that both regulatory action and action in UK healthcare systems more widely is needed.

The CHM considered that any regulatory actions should be proportionate, and that there are some patients seen in primary care for whom fluoroquinolones are an appropriate treatment option.

Conclusions of the review

The final recommendations were as follows:

- The CHM considered that it would be appropriate to strengthen warnings in the product information, so that fluoroquinolones (given by mouth, injection or inhalation) must not be used if other appropriate options are available.

- The CHM also supported updates to the product information regarding the description and the frequency statement for these events in line with available data.

- The CHM did not consider that there was enough evidence to take additional regulatory action on topical products (applied to a body surface such as skin or eyes) at this time.

- The CHM supported communications to remind UK healthcare professionals about this risk and the existing risk minimisation measures, and any additional UK action taken by MHRA as a result of this review.

- The CHM advised the MHRA to consider how routes for communication could maximise distribution of these safety messages, for example publications aimed at healthcare professionals.

- To increase the reach of safety communications, the CHM recommended working in partnership with relevant organisations with an interest in optimising the use of fluoroquinolones, so they are used in scenarios where the balance of benefits and risks is most favourable.

- The CHM also advised that the MHRA should liaise with appropriate stakeholders to explore whether additional alerts about the risk of potentially long-lasting or irreversible side effects associated with fluoroquinolones could be introduced in electronic prescribing systems used by healthcare professionals.

- The CHM considered that, in addition to actions that are part of the MHRA's regulatory remit, more scientific research is needed, including into the mechanisms by which fluoroquinolones cause these events and to develop a case definition for disabling and potentially long-lasting or irreversible side effects associated with fluoroquinolones.

Other regulatory actions to minimise risk, including a patient alert card, restriction of the clinical setting in which fluoroquinolones are used, written documentation of informed consent, or restriction of fluoroquinolones to life-threatening situations only, were not considered appropriate at this time by the CHM, because they would not be practical to implement, would unlikely to be effective and they could have harmful impacts on the UK healthcare system.

Action taken so far

The MHRA has taken additional regulatory action based on the findings of the review and the recommendations of the CHM. These actions are summarised in the table below.

CHM Recommendation	**Regulatory Action**
The CHM considered that it would be appropriate to strengthen warnings in the product information, such that fluoroquinolones must not be used if other appropriate options are available.	The product information for fluoroquinolones has been updated to state that they should only be used when other commonly recommended antibiotics are inappropriate. Situations where other antibiotics are considered to be inappropriate are where: • there is resistance to other first-line antibiotics recommended for the infection • other first-line antibiotics are contraindicated in an individual patient • other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped • treatment with other first-line antibiotics has failed
The CHM supported updates to the description and the frequency statement for these events in line with available data.	The description of disabling and potentially long-lasting or irreversible side effects in the safety information has been updated, to include more detail about the range of psychiatric symptoms that may occur as part of these reactions. These may include sleep disorders, anxiety, panic attacks, confusion or depression. Description of these disabling and potentially long-lasting or irreversible side effects has been moved from ‘very rare’ to the first bullet point in the ‘rare’ category in the Patient Information Leaflet (PIL) that comes with the medicine.
The CHM supported communications to remind UK healthcare professionals	A Drug Safety Update to remind healthcare professionals about the risks was published in

about this risk and the existing risk minimisation measures, and any additional UK action taken by MHRA as a result of this review. The CHM advised the MHRA to consider how routes for communication could maximise distribution of these safety messages, for example publications aimed at healthcare professionals.	August 2023 and a Drug Safety Update covering psychiatric side effects specifically was published in September 2023. To communicate the additional regulatory action, a Drug Safety Update was published in January 2024 and distributed through healthcare professional subscriber channels. This was published alongside a Press Release which was pitched to healthcare professional publications as well as national media to raise awareness.
To increase the reach of safety communications, the CHM recommended working in partnership with relevant organisations with an interest in optimising the use of fluoroquinolones, so they are used in scenarios where the balance of benefits and risks is most favourable.	Since the findings of the review were released, MHRA has been working with UK Healthcare Organisations such as The National Institute for Health and Care Excellence (NICE), British Infection Association (BIA) and UK Health Security Agency (UKHSA) to ensure relevant guidelines and advice is updated in accordance with the recommendations and to promote key safety messages.

Next steps

The MHRA will continue to work with healthcare professional organisations on the additional recommendations.

The MHRA will also work towards the CHM's recommendation to liaise with appropriate stakeholders to explore whether additional alerts about the risk of potentially long-lasting or irreversible side effects associated with fluoroquinolones could be introduced to electronic prescribing systems used by healthcare professionals.

The MHRA will continue to monitor the safety of fluoroquinolones and will take further regulatory action if this is appropriate.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulator of medicines, medical devices and blood components for transfusion in the UK. The MHRA is responsible for making sure these products meet acceptable standards for safety, quality and efficacy. The Commission on Human Medicines (CHM) advises the government about medicines safety. The CHM is independent – it is not part of the government or the pharmaceutical industry.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

Previous Public Assessment Reports on the safety of fluoroquinolones were published in 2018 by the European Medicines Agency.

This report presents the MHRA's review of safety data for fluoroquinolone antibiotics and expert advice on management of risks, as advised on by CHM. Changes have been made to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the review in 2023. The MHRA and CHM will continue to monitor the safety of fluoroquinolone antibiotics closely, however the information in this report will not be actively updated with new data or studies.

3. Background

3.1 Fluoroquinolones

Fluoroquinolones are a class of broad-spectrum antibiotics which inhibit synthesis of bacterial DNA by binding to topoisomerase enzymes. They were first developed in the 1980s by the addition of a fluorine atom to the core structure of the previously existing quinolone antibiotics (Andriole, 2005). No quinolone antibiotics are authorised in the UK. The fluoroquinolones currently authorised in the UK are ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, and ofloxacin. Norfloxacin products have been authorised in the UK in the past, but no norfloxacin products are currently authorised in the UK. Oral and intravenous fluoroquinolone products have indications for the treatment of a number of different types of infection, including respiratory tract infections, skin and soft tissue infections, and genital and urinary tract infections. For ciprofloxacin and levofloxacin oral products this includes an indication for the post-exposure prophylaxis and curative treatment of inhalation anthrax. Eyedrop and eardrop products are authorised for the treatment of ocular and ear infections, and an inhaled levofloxacin product (Quinsair) is authorised for chronic pulmonary *P. aeruginosa* infections in adults with cystic fibrosis.

In the UK fluoroquinolones are prescribed in both primary and secondary care. Data suggest that their use in primary care is often for urogenital tract or respiratory tract infection: in The Health Improvement Network (THIN) for England, between 2013 and 2015 the most commonly recorded indications for fluoroquinolones were urogenital tract conditions (28.3%), and respiratory tract or ear, nose, and throat conditions (14.1%) (Dolk and others, 2018), although a high proportion (43.0%) of prescriptions had no recorded diagnostic code for the indication.

3.2 Previous regulatory review

In February 2017 a European review (Article 31 referral procedure) was launched, to review the severity and persistence of long-lasting, disabling and potentially irreversible adverse drug reactions (ADRs) reported in association with fluoroquinolones, the impact of these safety concerns on the overall benefit-risk balance of fluoroquinolones, and the need for measures to minimise these risks (European Medicines Agency [EMA], 2018). This referral included an assessment of non-clinical data, intended to aid evaluation of the potential causal relationship between fluoroquinolones and these ADRs, as well as an assessment of spontaneous ADR reports from EudraVigilance, and published case reports. The available scientific literature was also reviewed, and then two population-based nested case-control studies were carried out to assess the risks of tendon rupture and peripheral neuropathy in association with systemic exposure to fluoroquinolones.

As part of the European review a public hearing was held on 13 June 2018, this included contributions from patient representatives, carers, and families, a pharmaceutical company, and healthcare professionals and academics. Supporting documents and a video recording of the public hearing are available on the EMA website.

In summary, the conclusions and outcomes from the referral were:

- Serious ADRs associated with the use of quinolones and fluoroquinolones can very rarely be long-lasting, disabling and potentially irreversible, and these risks are a class effect;

- Some indications which were considered to no longer have a positive benefit-risk balance were removed (for example prophylaxis of travellers' diarrhoea);

- Some indications (for example uncomplicated cystitis) were restricted, such that fluoroquinolones should be used only when it is considered inappropriate to use other antibacterial agents commonly recommended for these infections;

- Warnings were added to the product information:

    - Use of fluoroquinolones should be avoided in patients who have previously experienced serious ADRs in association with quinolone or fluoroquinolones;

    - Prolonged, disabling, and potentially irreversible serious ADRs affecting different, sometimes multiple, body systems have been reported. Fluoroquinolones should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice;

    - Tendinitis and tendon rupture may occur, and the risk is increased in older patients, those with renal impairment, solid organ transplant, or with concomitant use of corticosteroids;

    - Sensory or sensorimotor polyneuropathy has been reported, and patients should be advised to inform their doctor prior to continuing treatment if symptoms develop, in order to prevent the development of a potentially irreversible condition;

- Core elements of a Direct Healthcare Professional Communication (DHPC) were agreed;

- An EMA-funded Drug Utilisation Study (DUS) was planned to assess the impact of these risk minimisation measures by evaluating prescribing patterns in European countries.

This referral procedure received a European Commission (EC) final decision on 11 March 2019.

Updates to the product information for fluoroquinolones were implemented in the UK following the European review and EC final decision. The restrictions to the use of fluoroquinolones and warnings about the potential for disabling and potentially long-lasting or irreversible side effects were communicated to UK healthcare professionals in a Drug Safety Update (DSU) bulletin, published online on 21 March 2019. A UK Direct Healthcare Professional Communication (DHPC) was circulated to healthcare professionals, including GPs, in March 2019, this was accompanied by a patient sheet intended to help healthcare professionals deliver the advice to patients when prescribing fluoroquinolones (the patient sheet linked above has since been updated to reflect the outcomes of this review). An alert was also sent through the Central Alerting System to all NHS trusts, to be cascaded locally, this included a link to the Drug Safety Update.

3.3 Further UK review

Since the conclusion of the European review the MHRA has continued to receive reports of disabling and potentially long-lasting or irreversible ADRs in association with fluoroquinolones. The MHRA has also received correspondence expressing concerns about the safety of fluoroquinolones and the effectiveness of the current risk minimisation measures. This has been received from individual patients, members of the public, and healthcare professionals, and also from representatives of Fluoroquinolone Toxicity Support UK (FQTSUK), a patient support group for people experiencing ADRs in association with fluoroquinolones. Parliamentary questions have also been asked on these topics.

Additional evidence on the safety of fluoroquinolones and the effectiveness of measures to minimise the risk of disabling and potentially permanent side effects has become available since 2018, in the form of UK ADR reports, the results of the EMA-funded Drug Utilisation Study (DUS) of prescribing trends following the European review, and publications investigating disability and serious ADRs in association with fluoroquinolones. The results of the EMA-funded Drug Utilisation Study (DUS) of prescribing trends following the European review were on the agenda for the April 2023 meeting of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (EMA, 2023). Marketing Authorisation Holders (MAHs) for fluoroquinolones contacted the MHRA from 24 April 2023, informing the Agency that following the DUS results the PRAC had recommended a DHPC for systemic and inhaled fluoroquinolone antibiotics and the risk of persistent serious side effects and restrictions on use. The content of the DHPC was to provide a reminder to healthcare professionals about the current indications and restrictions for use for fluoroquinolones in the EU, it did not communicate any new regulatory actions. The DHPC

stated that the DUS suggests that fluoroquinolones may still be being used outside their authorised indications, but that due to the limitations of the study no definitive conclusions can be drawn. The DHPC was circulated in July 2023. The proposed distribution list included GPs, a number of different specialist prescribers, hospital and community pharmacists, and professional societies, with discretion for national regulatory agencies in which specialties should be included.

In view of the serious nature of these ADRs, the impact they have on patients, and the availability of new evidence since the European review, the MHRA has carried out a further UK review of fluoroquinolones. Patient engagement and inclusion of the patient voice have a central role in this review.

3.4 Patient engagement

In January 2023 the MHRA made Fluoroquinolone Toxicity Support UK (FQTSUK) aware it would be carrying out a UK review of the use of fluoroquinolones. Patients were invited to contact the MHRA by e-mail to contribute to the review. Up to 09 March 2023 the MHRA received e-mails from 100 patients and patient representatives expressing their interest in contributing to the review. In some instances, a patient and a representative of theirs both contacted the MHRA. A Yellow Card report had previously been submitted in connection with the ADRs mentioned by 61 of these patients and patient representatives. Where patients, who had not previously reported a Yellow Card, provided information about suspected side effects associated with a fluoroquinolone, this was recorded this as a new Yellow Card report (n=23). Patients who had not provided this information and who had not previously submitted a Yellow Card report were invited to do so. Correspondents were informed that a central part of the scope would be the effectiveness of current measures to reduce the risk of disabling and potentially permanent ADRs in association with fluoroquinolones, and were invited to provide comments on other aspects relating to the safety of fluoroquinolones they considered would be important to include. Fifty-three sets of comments were received in response to this invitation. Themes from written patient engagement are attached as Annex 1.

The MHRA also met with a group of 6 patients and carers, composed of representatives nominated by QTSUK plus other individuals who had given evidence at the EMA public hearing, in order to hear further from them about specific aspects of the safety of fluoroquinolones and measures to minimise risk that they considered it important for the MHRA to include in this review. The meeting with this group took place by video teleconference on 23 February 2023. Themes from the fluoroquinolones patient and carer meeting are attached as Annex 2. The same group of patient and carer representatives were invited to present their lived experiences at the May 2023 meeting of the CHM.

Key themes relating to the effectiveness of risk minimisation that emerged clearly from across the patient engagement activities were:

- Patients were concerned that healthcare professionals are not aware of the risks of fluoroquinolones;
- Patients have reported that healthcare professionals often do not believe patients who report these long-lasting, disabling, or potentially irreversible ADRs, and may be dismissive of patients who report them;
- More needs to be done to make healthcare professionals aware of the risks associated with fluoroquinolones;
- More need to be done to ensure patients are aware of the risks associated with fluoroquinolones;
- In view of the risks associated with them, the use of fluoroquinolones should be restricted;
- Patients are concerned about the lack of a recognised term or diagnosis for these ADRs, and the lack of effective treatment for these ADRs.

These aspects are considered as part of the review of the effectiveness of current risk minimisation measures for long-lasting, disabling, or potentially irreversible ADRs.

Other aspects relating to the safety of fluoroquinolones that were identified for inclusion in this review, taking into account patient and patients representative views, are:

- Frequency of long-lasting, disabling, or potentially irreversible ADRs;
- Topical fluoroquinolones and long-lasting, disabling, or potentially irreversible ADRs;
- Psychological impacts;
- Mechanisms underlying long-lasting, disabling, or potentially irreversible ADRs in association with fluoroquinolones;
- Potential for risks associated with concurrent or subsequent use of non-steroidal anti-inflammatory drugs (NSAIDs).

It is extremely important that the serious impacts that these ADRs have had, and continue to have, for patients is acknowledged during any review and that patient experiences are carefully considered as part of the assessment of all these areas.

4. MHRA Review

4.1 Effectiveness of current risk minimisation measures

4.1.1 Patient experiences

4.1.1.1 Awareness of risks among healthcare professionals

A key component of the current risk minimisation measures is the extent to which healthcare professionals are aware of the restrictions to the indications of fluoroquinolones and warnings about the potential for long-lasting, disabling, or potentially irreversible ADRs that were introduced in the UK in 2019. Awareness of these restrictions and warnings would be expected to limit the risk of ADRs by reducing the prescribing of fluoroquinolones. This would be as a direct consequence of healthcare professionals no longer prescribing fluoroquinolones in certain situations where their use had been previously been felt to be acceptable, for example for non-severe or self-limiting infections and some mild or moderate infections where alternative antibiotics can be appropriately prescribed instead. It might also be expected that healthcare professionals opt to prescribe an alternative antibiotic in preference to a fluoroquinolone, in situations where clinical guidance includes fluoroquinolones as one of several treatment options, due to their awareness of the risks associated with fluoroquinolones. For example, the ciprofloxacin Summary of Product Characteristics (SmPC) includes an indication for acute pyelonephritis, and the NICE guideline [NG111] lists ciprofloxacin as one of four first-choice oral antibiotics for this condition.[1] Patient experiences provide some insight on the potential level of awareness of the risks of fluoroquinolones among healthcare professionals. In the written patient engagement a significant number of patients (n=37 of 53 sets of comments on the scope of the review) expressed their concerns that, based on their personal experiences, awareness of long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones among healthcare professionals is low (see Annex 1). A number of these patients (n=12) also specifically mentioned that healthcare professionals have been dismissive when presented with concerns about these ADRs. Similar concerns were raised by patients and patient representatives at the fluoroquinolones patient group meeting (see Annex 2).

Fluoroquinolone Toxicity Support UK (FQTSUK) provided a document on 16 March 2023 containing descriptions of patient experiences. A version of this document, in which the names of people and places that could potentially identify individuals are redacted, was included in the paper sent to the CHM. This was an updated version of a document originally sent to the MHRA by FQTSUK in 2019. It included 50 sets of comments, collected

[1] Updated following this review with the caveat that it should be used only if other first-choice antibiotics are unsuitable.

by FQTSUK up to December 2020. These were collected to provide an indication of the level of awareness among UK healthcare professionals about risk minimisation measures for fluoroquinolones. The collection of both new and similar patient experiences by the group has steadily increased since this time.

Out of these 50 comments, 25 state that after the onset of the ADRs the patient had interactions with healthcare professionals who appeared to be unaware that fluoroquinolones were associated with long-lasting, disabling, or potentially irreversible ADRs. In 14 of these 25 comments it is clear that this happened after the UK regulatory communications in March 2019; in the remaining comments the interactions took place before March 2019, or the date was not specified in the quote provided. In 17 comments the patients stated that healthcare professionals were dismissive of fluoroquinolones being a cause of these ADRs. In at least 13 of these instances this occurred after the UK regulatory communications in March 2019, in some cases a substantial period of time after this date. There were 3 comments that specifically noted the efforts made by a healthcare professional to listen to the patient and to try to help.

One comment consisted of a list of the patient's interactions with healthcare professionals between April and November 2019, and the extent to which these healthcare professionals were aware of risks associated with fluoroquinolones. The list of 23 interactions with healthcare professionals includes 16 where the healthcare professionals were described as being receptive to information about the warnings that have been issued concerning fluoroquinolones, and 7 where healthcare professionals were described as not being receptive to this information when it was raised by the patient. Each instance of an interaction may have involved more than one healthcare professional.

A patient, who is also a healthcare professional, provided a document with a description of their experience of ADRs associated with ciprofloxacin. This was also provided to the CHM with any identifiable information having been redacted. This document included 15 examples of interactions with other healthcare professionals occurring since September 2019, and the extent to which they were aware of risks associated with fluoroquinolones. In 6 instances the patient described the other healthcare professionals as being aware of long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones, or accepting that his symptoms were ADRs related to fluoroquinolones. In 7 instances the other healthcare professionals had been previously unaware of this association. In 2 instances it was not clear whether the other healthcare professionals were previously aware of these ADRs. Each instance may have involved an interaction with more than one other healthcare professional.

The accounts of healthcare professional awareness about the risks associated with fluoroquinolones referenced above come from the experiences of patients who have experienced ADRs associated with fluoroquinolones. They are not a random sample of UK

healthcare professionals, and we do not have comments about the awareness among healthcare professionals from all the patients who have contacted the MHRA to report their experiences. These data cannot be used to quantify the extent to which healthcare professionals are aware of the risk associated with fluoroquinolones, and the associated regulatory actions. They do however strongly suggest that there are healthcare professionals who have limited awareness of these risks.

4.1.1.2 Provision of information about risks to patients

A key component of risk minimisation is the information given to patients about the potential ADR associated with medicines. At the time of this review, Patient Information Leaflets (PILs) for systemic fluoroquinolone products included a warning in section 2 (before you take) stating that patients should not take a fluoroquinolone if they have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. This warning was introduced as part of the product information updates in 2019. Section 2 and section 4 (side effects) of the PIL also contain a warning about, and description of, the prolonged, disabling and potentially irreversible serious side effects. However, the structure and length of the PIL meant that this information did not appear early in the PIL content, for example in some PILs when viewed in pdf format it appears on the third page and later.

Among the 53 sets of written patient comments received, a significant number of patients (n=21) expressed their views that patients need to be made more aware of the risk of long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones (Annex 1). A number of these patients expressed a view that informed consent should be obtained when prescribing (n=11). Some comments that the patient information leaflet should be updated (n=4), or that warnings about risks should be placed on the boxes of fluoroquinolones (n=3).

In the patient experiences document provided by FQTSUK that was included in the paper reviewed by the CHM, the comments relate mainly to the nature of the ADRs experienced by patients, and their experience of interacting with healthcare professionals. One comment specifically asks why the benefits or risks of fluoroquinolones were not fully explained.

An online survey was provided by a patient as part of the engagement work for this review, which included responses from 30 respondents to 69 statements (Pol.is survey). This was described as having “surveyed a number of fluoroquinolone-damaged patients in their own words”; the method used to select these 30 patients was not specified, and the MHRA has not requested further details from the patient who provided the link to the survey results. It is unlikely that these 30 patients represent a random sample of patients experiencing of long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones, and there is therefore potential for selection bias and response bias to have had an impact on the responses. The respondents did not all provide responses to every statement. In

response to the statement “I was adequately warned of the damage that fluoroquinolones would do” 4% agreed, 88% disagreed, and 8% passed (25 responses total).

4.1.1.3 Availability of treatment

The availability of treatment is relevant to risk minimisation, such that if no treatments are available for an ADR the only way to limit its impact on patients is to prevent its occurrence. In the written patient engagement a number of patients (n=10) noted that treatments for long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones are lacking (Annex 1). The lack of treatment options was also raised by patients and patient representatives at the fluoroquinolones patient group meeting, with reference to a review article by Michalak and colleagues which reviews mechanism(s) by which fluoroquinolones can cause long-lasting, disabling, or potentially irreversible ADRs (Michalak and others, 2017). As previously mentioned, Michalak and colleagues noted that effective treatments are lacking, and proposed 6 areas for further exploration as potential treatments for patients affected by these ADRs (Michalak and others, 2017). As part of our patient engagement, a publication which proposes a number of possible treatments for these ADRs was mentioned (Pieper, 2021) by patients.

It is challenging to formulate treatment plans when the condition and its pathogenesis have not been fully elucidated. Michalak and others, (2017) acknowledge limitations in current understanding of fluoroquinolone toxicity, yet nevertheless indicate potential areas for therapeutic intervention. These proposals are presented as broad themes: “reduction of the oxidative stress”, “restoring reduced mitochondrial potential”, “supplementation of uni- and bivalent cations that are chelated by fluoroquinolones”, “supporting the mitochondrial replication in the cell”, “removing fluoroquinolones permanently accumulated in the cells”, and “regulating the disturbed epigenetics and enzyme activities”. Similarly, Pieper (2021) gives another overarching theme, “antioxidative therapy”, as the core aspect of treatment for fluoroquinolone toxicity.

Many of the suggested therapies in Michalak and others (2017) and Pieper (2021) appear to be supplements that can be bought over the counter such as MitoQ, vitamins C and E, and the trace elements of zinc, manganese copper, cobalt, selenium. Proposed treatments regimes are non-specific, with no practical detail provided on what the therapy entails. There is limited or no information given on posology, formulation, or method of administration. Michalak and others (2017) notes that efficacy of potential treatments is low, however no data relating to efficacy are referenced. Indeed, there is a striking lack of evidence in both publications regarding efficacy or safety in either humans or in animal studies, with an absence of even low levels of evidence such as case reports.

Both publications put forward theoretical reasoning to explain why these treatments may work. For example, Michalak and others (2017) propose cyclosporine A and metformin as

possible therapeutic agents because of their postulated ability to close mitochondrial permeability transition pores and protect against oxidative stress. Both Michalak and others (2017) and Pieper (2021) quote an *in vitro* study of cultured human Achilles tendon cells that found lower oxidative stress and stabilized mitochondrial membrane potential in cells treated with MitoQ (an antioxidant that targets mitochondria). Both authors also suggest pyrroloquinoline quinone as a possible treatment option for fluoroquinolone toxicity and consider the therapeutic mechanism of action to be the promotion of mitochondrial replication and protection against oxidative stress. No adequate evidence is presented to support these assertions that the suggested therapies are able to act as treatments for fluoroquinolone toxicity.

Currently therefore there is no robust evidence for any of the proposed therapeutics for the treatment of fluoroquinolone toxicity, and most of the treatment proposals are clearly at hypothetical stages.

At the time of this review, the product information for systemic fluoroquinolones advised that the products should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and that patients should be advised to contact their prescriber for advice in this situation. As part of patient engagement for this review it was raised that this wording has been misinterpreted as implying a greater availability of treatment for the ADRs than is currently the case.

4.1.2 UK ADR data

4.1.2.1 Yellow Card database search

UK spontaneous Yellow Card report data from the Sentinel database were extracted and assessed to provide data on the occurrence of long-lasting, disabling, or potentially irreversible ADRs in the UK from the time period since the conclusion of the EU review in November 2018 and from the implementation of UK communications in March 2019.

A widely accepted case definition for long-lasting, disabling, or potentially irreversible ADRs in associated with fluoroquinolones is not in use. As part of patient engagement, a publication that proposes a possible definition for these ADRs, using the term Fluoroquinolone-Associated Disability, was mentioned (Pieper 2021). There does not appear to be any clear evidence base or validation for this tool. Nor does it appear adequately sensitive or specific to appropriately identify and diagnose a patient with fluoroquinolone toxicity. These areas require further, higher quality research according to the author.

A 2021 study assessed Food and Drug Administration (FDA) Adverse Event Reporting System data, and approximately 300 survey responses from a social network, and aimed to

assess the incidence of functional gastrointestinal disturbances in association with fluoroquinolones (Cannizzaro and others, 2021). The authors concluded that gastrointestinal disorders other than nausea, vomiting, and diarrhoea may occur in association with fluoroquinolones and be long-lasting, and the title of the publication, “New Criterion for Fluoroquinolone-Associated Disability Diagnosis: Functional Gastrointestinal Disorders” implies that the authors consider that these ADRs could form part of a case definition for disabling or long-lasting ADRs associated with fluoroquinolones, although they do not explicitly state this in their conclusions.

In view of the lack of a widely accepted case definition, and the possibility that signs and symptoms that could be considered necessary or sufficient to identify patients experiencing disabling and potentially long-lasting or irreversible ADRs are still being identified, it would not be appropriate to restrict a search for relevant reports to a specific list of MedDRA term, or combination of terms. Such a restriction might not identify reports of interest with sufficient sensitivity, and therefore the approach to searching the MHRA Yellow Card database was to use a broad set of search criteria expected to have high sensitivity, followed by manual review of the reports, to categorise these according to whether they appeared to be consistent with a report of disabling or long-lasting ADRs.

The database search was conducted to return reports meeting the following criteria:

- UK spontaneous ADR reports;
- A fluoroquinolone (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, or ofloxacin) as a suspect drug ingredient;
- First received by the MHRA between 15 November 2018 and 22 January 2023 (based on the date the European review concluded and the date the extraction was carried out);
- Seriousness flag for disabling OR ADR outcome Resolved with sequalae OR duration of at least one ADR ≥30 days OR case narrative include one of the following phrases: “disab”, “debilit”, “permanent”, “continu”, “long”, “floxed”, “floxxed”, “toxic”, “FQAD” “poison” OR the ADR coded is “Adverse drug reaction”, "Adverse event", "Adverse reaction" (to allow manual review of awaiting reclassification of these non-specific terms).

This search process was similar to that used in the European review (pages 8 & 9)(EMA, 2019), although the EMA search did not include a search of the case narrative for potentially relevant phrases, or a search for reports with a non-specific ADR term (included here to increase sensitivity).

This search returned at total of 750 reports. These were then assessed at individual report level, to categorise them according to whether the case was consistent with the disabling and potentially long-lasting or irreversible ADRs described in the current product information and associated regulatory communications. In brief, the type of ADRs was assessed as being: 1) consistent with the disabling and potentially long-lasting or irreversible ADRs, 2) unclear (for example if a single non-specific ADR was reported, with information lacking on whether a diagnosis was made or other ADRs were present), 3) distinct from these ADRs (for example ADRs representing an identifiable and distinct entity, such as Stevens-Johnson syndrome). The duration and impact of the ADRs was also assessed as being: 1) disabling and/or long-lasting (less than 30 days duration), 2) having an impact and duration that were unclear based on the information provided, 3) not disabling or long-lasting.

Reports were then categorised according to whether they were consistent with a report of disabling and potentially long-lasting or irreversible ADRs, as set out in table 1. Reports could also be manually assigned to a category of "Not relevant", for example if the report was a duplicate of another report in the extraction, or if on review it was clear that the patient did not receive a fluoroquinolone. This review process was similar to that used in the European review (pages 8 & 9) (EMA, 2019), although the European review assessed reports based on whether "confounding factors" were identified (specifying other medicines, or underlying diseases), and the review focussed on reports considered "not confounded". Reports were not excluded in this way from this MHRA review.

Table 1: process for categorisation of reports from the Yellow Card Scheme

		Type of ADRs		
		ADRs consistent with those of interest	**Type of ADRs unclear**	**ADRs distinct from those of interest**
Duration/impact	**Disabling and/or long-lasting ADRs**	Consistent	Potentially consistent	Not consistent
	Impact and duration unclear	Potentially consistent	Cannot be categorised	Not consistent
	Not disabling OR long-lasting	Not consistent	Not consistent	Not consistent

Due to the resource-intensive nature of the review process, reports were reviewed from a subset of the initial data extraction, using a time period, from 01 January 2020 to 22 January 2023. This time period included 553 reports in total. Of these, 31 were categorised as "Not relevant," mainly because they were duplicates of another report. The categorisations of the remaining 522 reports are summarised in table 2. A total of 290

reports were categorised as “Consistent” or “Potentially consistent” with reports of disabling and potentially long-lasting or irreversible ADRs.

Table 2: categorisation of reports from the Yellow Card Scheme according to whether they appeared consistent with disabling and potentially long-lasting or irreversible ADRs

	Year initial report was received				
	2020	**2021**	**2022**	**2023***	**Total**
Consistent	83	81	87	0	251
Potentially consistent	10	13	16	0	39
Not consistent	41	108	63	7	219
Cannot be categorised	0	5	8	0	13
Total	134	207	174	7	**522**

*Data for 01 January 2023 – 22 January 2023 only

A further data extraction was also carried out for fatal reports, using the criteria:

- UK spontaneous ADR reports;
- A fluoroquinolone (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, or ofloxacin) as a suspect drug ingredient;
- First received by MHRA between 01 January 2020 to 22 January 2023;
- Fatal outcome.

This returned 15 reports, including 1 categorised as “Consistent” and 1 categorised as “Potentially consistent” with being reports of disabling and potentially long-lasting or irreversible ADRs. Reports with fatal outcomes are discussed in section 4.1.2.4.

In addition, existing or newly created Yellow Card reports from patients who contacted the MHRA in writing to contribute to the review were included, regardless of whether they occurred within the review time period. This led to the inclusion of 57 additional reports, of which 54 were categorised as “Consistent” and 2 were categorised as “Potentially consistent” with being reports of disabling and potentially long-lasting or irreversible ADRs. One report was categorised as “Not consistent.” Many of these reports were received in 2023 but concerned ADRs that started in an earlier year – the date the ADRs first began was used to assign these reports to a year, rather than year of reporting.

When the additional “Consistent” or “Potentially consistent” reports with fatal outcomes (n=2), and the additional “Consistent” or “Potentially consistent” reports from patient engagement (n=56) are included, the total number of reports categorised as “Consistent” or “Potentially consistent” was 348. This includes 303 reports from the time period 01 January 2020 to 22 January 2023 (which were therefore reported after the UK regulatory action in March 2019).

In the set of 348 reports age was reported in 89.1% (310/348). Mean age was 53.2 years (SD 18.3), median age was 68 years (IQR 38 – 51). These figures should not be treated as unbiased estimates of the age of patients who experience these ADRs, due to possible reporting biases, for example patients in certain age groups have different probabilities for reporting an ADR. For this reason any attempt to determine if these ADRs are occurring disproportionately in particular age groups would have significant limitations. It is certainly the case that these ADRs can occur across a range of ages. Data on patients' sex was included 98.3% (342/348) of reports. Of the 342 ADR reports that included data on sex, 44.7% (n=153) were in females, 55.3% (n=189) in males.

The identification of relevant reports from the Yellow Card scheme in this way has important limitations that should be noted:

- Under-reporting;
- Search sensitivity;
- Accuracy of categorisation.

Under-reporting

Under-reporting is a well-known limitation of spontaneous reporting systems. The extent of this under-reporting may be variable and can be influenced by many factors including the seriousness of the ADRs, how easy they are to recognise, and the extent of usage for the medicine in question. Reporting can also be stimulated by promotion and publicity about a medicine. The extent of under-reporting is typically unknown for any medicine and ADR combination.

A systematic review of 37 studies investigating the extent of under-reporting from spontaneous ADR reporting schemes concluded that it was not possible to estimate the level of under-reporting in general, but that more than 90% of ADRs were likely to be unreported (Hazell and Shakir, 2006). It is important to consider the potential impact of under-reporting when analysing spontaneous ADR, but it is not reliable to apply a fixed multiplier to the number of reports received and treat the result as an accurate estimate of the number of ADRs that have actually occurred.

Evidence from patient experiences (section 4.1.1) suggests that there are healthcare professionals who are not aware that fluoroquinolones are associated with long-lasting, disabling, or potentially irreversible ADRs. This lack of awareness would be expected to contribute to under-reporting by healthcare professionals. One patient who reported experiencing disabling ADRs in association with a fluoroquinolone also specifically mentioned that having later seen their medical records, only one of the many symptoms

they experienced (nausea) had been recorded – this provides a single instance where under-recording of ADRs in medical records was confirmed, and it appears that these ADRs were also not reported to the Yellow Card scheme by the healthcare professional. This is a single instance and does not allow the extent of under-reporting to be quantified, but it does provide a clear example of under-recording of ADRs occurring.

The introduction of patient reporting via the Yellow Card scheme in 2008 provides another route for the MHRA to receive reports for suspected ADRs that may not have been recorded or reported by healthcare professionals. However members of the patient group specifically noted that they had not personally been aware of the Yellow Card scheme, and it is plausible that there is under-reporting of these ADRs by patients for this reason. A Yellow Card report had previously been submitted in connection with the ADRs mentioned by 61 out of 100 patients and patient representatives who contacted the MHRA as part of the patient engagement for this review. At least one patient who contacted the MHRA noted that they had been too unwell when their ADRs first occurred to report them, and this may apply to other patients affected by these ADRs. These figures should not be used to attempt to quantify the extent of under-reporting, as there will be patients who have experienced these ADRs but have not contacted the MHRA in connection with the review. It does however confirm that under-reporting of these ADRs has occurred.

In the online Pol.is survey provided by a patient as part of the engagement work for this review, 26 respondents responded to the statement “I have filed a Yellow Card to the MHRA about my reaction to these antibiotics.”; 38% agreed, 38% disagreed, and 23% passed (Pol.is survey).

Search sensitivity

The number of relevant reports identified in the Yellow Card database will also depend on the sensitivity of the search used. The search strategy was developed based on the previous search strategy used in the European review, with the addition of a search of report narratives, intended to improve sensitivity. It is possible that additional reports from within the time period might be identified if a broader search was used. For example, if the search criterion “seriousness flag for disabling” was extended to “any seriousness flag” (this would include, for example, “Reporter considered serious” and “Other medically significant” flags). This would have greatly increased the number of reports requiring individual review, an exploratory search suggests by more than 2-fold, and this approach was not used, for practical reasons.

To explore the impact of a wider search strategy, a random sample of 100 of the reports that were additionally returned if the search criterion “seriousness flag for disabling” was extended to “any seriousness flag” were categorised. The categorisations were as follows: 8 “Consistent,” 33 “Potentially consistent,” 55 “Not consistent,” 4 Cannot be categorised. This expanded search therefore identified some additional “Consistent” or “Potentially

consistent” reports, but the proportion of these was lower than in the more specific search strategy as used for this review.

Accuracy of categorisation

The accuracy of how reports were categorised according to their consistency with a long-lasting, disabling, or potentially irreversible ADRs is a third important potential limitation. The consistency of the ADRs with those of interest was assessed using a conservative approach, and a report would only be considered “Not consistent” if the ADRs were clearly distinct from long-lasting, disabling, or potentially irreversible ADRs (for example a single identifiable and distinct ADR such as Stevens-Johnson syndrome) and/or if the report details made it clear that the ADRs did not have a disabling impact and did not last for more than 30 days. Cases categorised as “Not consistent” are not likely to have been misclassified.

Reports were classified as “Consistent” based on the presence of ADRs consistent with those identified in previous regulatory review, including but not limited to tendinopathies, musculoskeletal pain, neuropathies, sensory disturbances, along with disabling or long-lasting impact. The “Consistent” category could include some reports where one or more of these symptoms was present, but the overall picture differed from typical reports of long-lasting, disabling, or potentially irreversible ADRs. This category could also include some reports of tendon ruptures and tendinopathies that were disabling in their impact, but not accompanied by other symptoms, and resolved according to a timescale typical for these events. There were 65 reports in total from the set of 348 “Consistent” or “Potentially consistent” reports that reported terms relating to tendinopathies only (from the Tendon disorders or Muscle, tendon and ligament injuries MedDRA Higher Level Term groupings only). Of these, 19 had patients as the original reporter, and 46 had healthcare professionals as the original reporter. It should be noted that while some of these report Achilles tendonitis only, some report tendonitis without specifying the number or site of affected tendons, while some report tendonitis and make it clear that this affected multiple tendons and was prolonged and disabling. The time to onset of tendinopathies in association with fluoroquinolones is reported in the literature. A 2001 review that included 98 case reports of tendon injury in association with fluoroquinolones reported a mean time to onset of symptoms of 17.6 days, with substantial variability (standard deviation 19.5 days) (Khaliq and Zhanel, 2003). There could be some bias if the time to onset influences the probability of a case report being published, however a similar and similarly variable time to onset (13 days, range 1 – 90 days) for Achilles tendinitis has been reported in observational studies, for example in the study by van der Linden and colleagues (van der Linden and others, 1999).

The time to onset of symptoms of disabling and potentially long-lasting or irreversible ADRs is also variable in spontaneous reports. It is therefore possible that in some cases additional

symptoms appeared after the initial Yellow Card report was submitted, and follow-up information on the subsequent outcome is not always available. It also is possible in some of these reports that other ADRs were present at the time of reporting, but not reported – noting that many patient experiences describe healthcare professionals being aware of tendinopathies in association with fluoroquinolones, but not aware of other potential ADRs. Reports with a tendinopathy as the only ADR cannot be confidently excluded from those representing long-lasting, disabling, or potentially irreversible ADRs. And the impression provided when reviewing the 348 cases at the report-level is that the majority of the "Consistent" reports report multiple ADRs with long-lasting and disabling impacts.

Some reports categorised as "Potentially consistent" might not truly represent reports of long-lasting, disabling, or potentially irreversible ADRs, if more complete information was available. For example this category may include some reports of tendonitis where it was not clear whether the impact was disabling or whether the ADRs were long-lasting; such a report would be "Potentially consistent" in the absence of follow-up information to confirm the impact and eventual outcome, but it is possible that in some reports of this type the ADRs were in fact not disabling and resolved within 30 days. But it is also possible that some reports of this type that are lacking follow-up information would be categorised as long-lasting and therefore "Consistent" if this information became available.

Reports where the type of the ADRs, their impact, and duration were all unclear were placed in the "Cannot be categorised" group, however this group was small (13/522 for the initial data extraction, table 2) and misclassification here is unlikely to have had a significant impact.

This review did not include a step where reports were excluded on the basis of "confounding" factors, as was done in the European review. However, the impression from assessors who carried out the report-level review is that the reports, especially those submitted by patients, were well-documented. The presence of potential alternative explanations for the ADRs appeared infrequent among the "Consistent" and "Potentially consistent" reports.

4.1.2.2 Risk minimisation and risk factors in Yellow Card reports

In terms of data on the effectiveness of risk minimisation measures, these reports were assessed to determine whether the reported indication was consistent with the SmPC, and whether risk factors for ADRs were present. The risk factors assessed were chosen for consistency with the data gathered in the Drug Utilisation study: risk factors for aortic aneurysm or dissection; risk factors for tendon rupture; concomitant corticosteroids. The documentation of a previous serious ADR in association with a quinolone or fluoroquinolone was also assessed.

The presence of these factors in 303 reports from the time period 01 January 2020 to 22 January 2023 was as follows:

- Indication consistent with the SmPC: yes 50.2% (152/303), no 16.5% (50/303), 21.1% unclear (64/303), no data 12.2% (37/303);
- Risk factors for aortic aneurysm or dissection present: yes 5.0% (15/303), no 92.7% (281/303), 2.3% unclear (7/303);
- Risk factors for tendon rupture present: yes 47.2% (143/303), no 48.8% (148/303), 4.0% unclear (12/303);
- Concomitant corticosteroids: yes 14.5% (44/303), no 85.1% (258/303), 0.3% unclear (1/303);
- Previous serious ADRs in association with a quinolone or fluoroquinolone: yes 2.3% (7/303), no 97.4% (295/303), 0.3% unclear (1/303)

It is notable that the indication was only clearly consistent with the SmPC in approximately half the reports. The proportion where the indication was not reported or was unclear (for example because the indication was exacerbation of COPD but no information was given about whether other antibiotics were considered inappropriate) was high, approximately 33% across these categories. Instances of the indication not being consistent with SmPC (16.5%) include, for example, uncomplicated urinary tract infections or otitis externa. Because the proportion of reports with unknown or unclear indications is high, and because these reports are not necessarily a representative sample of prescribing instances (due to potential reporting biases) the proportions of indications consistent or not consistent with the SmPC from Yellow Card reports cannot be extrapolated to wider UK prescribing. However, prescribing of fluoroquinolones for indications not consistent with the current regulatory position on their indications is clearly occurring in the UK since 2019, and potentially this represents a significant proportion of prescriptions, although this cannot be quantified from these data.

The risk of aortic aneurysm or dissection in association with fluoroquinolones was communicated to UK healthcare professionals via a Drug Safety Update in 2018, based on data from epidemiological and non-clinical studies. The SmPCs for fluoroquinolones state that they should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or heart valve disease, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection and heart valve regurgitation/

incompetence (e.g. connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis). The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

The proportion of reports which recorded one of these risk factors was low, which is consistent with the low rate of prescribing in patients with these risk factors in the DUS results (see section 4.1.3.2). Because of the different data sources and differences in the definition of the risk group the Yellow Card data cannot be directly compared with the DUS data.

The proportion of reports which recorded a risk factor for tendon rupture, according to those listed in the SmPC, was high. These factors included age 60 years and over, renal impairment, solid organ transplant, concomitant corticosteroids. A low rate of prescribing in patients at increased risk of tendon rupture was found in the DUS results (see section 4.1.3.2). Prescribing of concomitant steroids was present in 14.5% of ADR reports. There is a warning in section 4.4 which states that concomitant use of corticosteroids should be avoided, due to the increased risk of tendonitis and tendon rupture. This risk has been confirmed by epidemiological data from a UK population (Morales and others, 2019). A low rate of prescribing of recent concomitant corticosteroids was found in the DUS results (see section 4.1.3.2). This difference between a low rate in the DUS and a high proportion in the Yellow Card reports for both patients at risk of tendon rupture, and those with recent or concomitant corticosteroid use, would be consistent with the increased risks leading to these groups appearing disproportionally more in Yellow Card reports compared with the underlying population of all patients prescribed a fluoroquinolone.

A number of factors were raised during patient engagement, as potentially representing risk factors for long-lasting, disabling, or potentially irreversible ADRs (Annex 1, Annex 2). These included use of steroids and renal impairment, which are specified as risk factors for tendinopathies in the product information and discussed above and in the DUS results. Concurrent or subsequent use of NSAIDs was also raised, this is specially included in the scope of this review, see section 4.6.

The other potential risk factors have been considered as part of this review, with a focus on whether there is sufficient evidence to conclude that these factors increase the risk of long-lasting, disabling, or potentially irreversible ADRs occurring, or could lead to these ADRs being more severe if they do occur. Whether the available evidence is sufficient to warrant changes to the current product information was also considered. In all cases preliminary assessment concluded that the evidence is currently insufficient to conclude that changes to the existing product information are warranted. The MHRA commits to further review as part of established pharmacovigilance processes to further investigate these preliminary assessments and document the conclusions.

In general, regarding potential risk factors for long-lasting, disabling, or potentially irreversible ADRs, it is important to note that the existing product information for fluoroquinolones states that these ADRs have been reported in patients irrespective of their age and pre-existing risk factors, and this is confirmed by data from patient experiences and Yellow Card reports. These include instances of these ADRs occurring in patients with no previous medical history. Therefore, extending the list of risk factors mentioned in the product information, if sufficient evidence is found to justify their inclusion, would have limitations as a means of minimising risks. Patients without these factors would still be exposed to the risk of long-lasting, disabling, or potentially irreversible ADRs when taking a fluoroquinolone.

4.1.2.3 Characterisation of spontaneous ADRs

Long-lasting, disabling, or potentially irreversible ADRs are described in the UK SmPCs for fluoroquinolones, which include the following warning in section 4.4 (as of the time of this review):

Prolonged, disabling and potentially irreversible serious adverse drug reactions

> *Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. [INN] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.*

The SmPCs include a similar description of the nature of these ADRs in section 4.8:

> *Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).*

The ADRs reported in the set of 348 “Consistent” and “Potentially consistent” reports from the Yellow Card database search described in section 4.1.2.1 were extracted to determine the symptoms reported, and the extent to which these are consistent with the current description of these events in the product information. There were 2,313 ADR terms

reported across 348 reports (mean 6.6 terms per report). In total 531 different MedDRA terms were reported at the MedDRA Preferred Term (PT) level. Many of these were reported in a small number of reports; 372 of the terms appeared in only 1 or 2 reports. The MedDRA terms which appeared most frequently are summarised in table 3.

Table 3: ADRs reported in 10 or more reports from 348 Consistent and Potentially consistent Yellow Card reports

MedDRA System Organ Class (SOC)	MedDRA Preferred Term (PT)	Number of PTs reported	Included in current SmPC description? (including synonyms and related terms, and secondary events)
Musc	Tendonitis	106	Yes
Musc	Arthralgia	96	Yes
Musc	Tendon pain	79	Yes
Genrl	Fatigue	59	Yes
Musc	Pain in extremity	57	Yes
Musc	Myalgia	53	No
Nerv	Paraesthesia	53	Yes
Nerv	Neuropathy peripheral	46	Yes
Psych	Anxiety	45	No
Ear	Tinnitus	40	No
Psych	Insomnia	35	Yes
Genrl	Pain	32	Non-specific
Musc	Muscular weakness	32	No
Nerv	Dizziness	29	No
Psych	Depression	29	Yes
Nerv	Hypoaesthesia	28	No
Musc	Tendon disorder	27	Yes
Inj&P	Medication error	25	No
Nerv	Headache	25	No
Nerv	Neuralgia	25	No
Card	Palpitations	24	No
Inj&P	Tendon rupture	24	Yes
Genrl	Asthenia	23	No
Musc	Back pain	22	Yes
Gastr	Nausea	21	No

MedDRA System Organ Class (SOC)	MedDRA Preferred Term (PT)	Number of PTs reported	Included in current SmPC description? (including synonyms and related terms, and secondary events)
Genrl	Adverse drug reaction	21	Non-specific
Musc	Muscle spasms	21	No
Musc	Muscle twitching	19	No
Nerv	Burning sensation	19	Yes
Gastr	Diarrhoea	17	No
Genrl	Feeling abnormal	17	Non-specific
Nerv	Tremor	16	No
Inj&P	Tendon injury	15	Yes
Genrl	Peripheral swelling	14	No
Musc	Musculoskeletal stiffness	14	Yes
Eye	Visual impairment	13	Yes
Genrl	Gait disturbance	13	Yes
Musc	Muscle atrophy	13	No
Genrl	Chest pain	12	No
Genrl	Malaise	12	Non-specific
Musc	Joint stiffness	12	Yes
Musc	Joint swelling	12	No
Nerv	Balance disorder	12	No
Resp	Dyspnoea	12	No
Eye	Vision blurred	11	Yes
Psych	Confusional state	11	No
Musc	Joint noise	10	Yes
Musc	Neck pain	10	Yes

Many of the symptoms most frequently reported in the set of 348 “Consistent” and “Potentially consistent” reports are specifically mentioned in the description in the current product information, for example tendonitis, fatigue, and neuropathies. Some symptoms are not specially mentioned in the product information but could be covered by terms that are included. For example, joint noise is not specifically listed, but is a symptom of tendonitis. Some of the symptoms are non-specific, for example pain and feeling abnormal. The most commonly reported symptoms that do not feature in the current description of prolonged, disabling and potentially irreversible serious adverse drug reactions include myalgia, anxiety, tinnitus, muscular weakness, dizziness, and hypoaesthesia.

The outcome of the ADRs in the set of 348 “Consistent” and “Potentially consistent” reports, at the time of the most recently received information for each report, was:

- 303 reports in which effects of ADRs were ongoing (at least one ADR outcome was Not recovered/not resolved, Recovering/resolving outcome, or Recovered/resolved with sequalae);
- 27 reports where the outcome for all ADRs was reported as unknown;
- 13 reports in which the only known outcomes for ADRs were recovered;
- 5 reports with a fatal outcome (see section 4.1.2.4)

In the 303 reports with ongoing ADRs the duration was calculated from the information in the reports. This is a minimum known duration, based on the most recently received information reporting the ADRs as ongoing. There were:

- 149 reports that had been ongoing for less than 1 month,
- 48 that had been ongoing for between one and less than 3 months,
- 28 that had been ongoing for between 3 and less than 6 months,
- 36 that had been ongoing for between 6 months and less than one year,
- 65 that had been ongoing for between one year and less than 5 years,
- 15 that had been ongoing for between 5 years and less than 10 years, and
- 7 that had been ongoing for 10 or more years.

These reports are not a random sample of all patients who experience disabling or long-lasting ADRs in association with fluoroquinolones, and the time point at which follow-up information on outcome is available will vary between reports. These data cannot be assumed to provide unbiased estimates of the proportion of different outcomes or the duration of these ADRs. But they clearly show that long-lasting ADRs occur, with 199 reports with ADRs ongoing at least 1 month after onset, and 123 reports with ADRs ongoing at least 6 months after onset, and 87 reports with ADRs ongoing at least 1 year after onset.

Published case reports concerning long-lasting, disabling, or potentially irreversible ADRs are limited. Golomb and colleagues published a case series of 4 previously healthy patients who experienced serious and persistent ADRs with multiple symptoms in association with

fluoroquinolones (Golomb and others, 2015). These cases report symptoms that are generally consistent with the UK spontaneous ADR data from the Yellow Card scheme.

It is important to note the impact of these ADRs on patients. Out of the set of 348 “Consistent” or “Potentially consistent” reports, 311 were recorded as serious, 218 or these were recorded as disabling. The testimonies provided by patients in written engagement and at the 23 February 2023 meeting, in Yellow Card report narratives, and in the quotes in the patient experiences document provided by FQTSUK include many examples where these ADRs have profound consequences for patients’ lives, including impacts on activities of daily living, the ability to work, and family life and relationships.

As well as impacts on those experiencing the ADRs, and for family members who in some cases have become carers, the impacts on the NHS were raised by patients. Detailed estimation of the costs to the NHS associated with these ADRs is outside the MHRA’s remit, but in general it can be noted that clinical and financial impact of ADRs is substantial. A study conducted between 2001 and 2002 in two UK hospitals found 6.5% of admissions were related to ADRs, and projected annual costs to the UK heath service were £466 million (Pirmohamed and others, 2004).[2] Some patients affected by long-lasting, disabling, or potentially irreversible ADRs in association with fluoroquinolones have had substantial contact with NHS services subsequently, to investigate and in some cases to attempt to treat the symptoms.

The nature of these long-lasting, disabling, or potentially irreversible ADRs was raised at the patient group meeting, noting the variable time to onset of these ADRs (which may hinder recognition and reporting), and the possibility that there are risk factors for these ADRs that are not mentioned in the current product information (discussed in section 4.1.2.2). The variability in onset times was noted as part of the safety communications issued in the UK in 2019.

The potential for gastrointestinal ADRs to form part of the symptoms of long-lasting, disabling, or potentially irreversible ADRs was also raised in patient engagement, including citing a study of the effect of antibiotics on salivary and faecal microbiomes (Zaura and others, 2015), a study of spontaneous ADR and survey data proposing that gastrointestinal disorders may occur in association with fluoroquinolones and be long-lasting (Cannizzaro and others, 2021), and a review article which proposed effects of fluoroquinolones on the vagus nerve as a mechanism for them to affect the gastrointestinal tract (Freeman and others, 2021). An observational study conducted in Taiwan that reported an association

[2] Post note: Osanlou R, Walker L, Hughes DA, et al. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions BMJ Open 2022;12:e055551. Doi: 10.1136/bmjopen-2021-055551

between fluoroquinolones and gastrointestinal perforation, not specifically in the context of long-lasting ADRs, was also cited (Hsu and others, 2017).

The set of 348 “Consistent” or “Potentially consistent” Yellow Card reports included 65 reports (18.7%) that reported at least one ADR term from the MedDRA Gastrointestinal disorders System Organ Class (SOC). The most commonly reported terms from this SOC were nausea (n=21), diarrhoea (=17), and abdominal pain upper (n=8) and abdominal pain (n=7). Some gastrointestinal disorders are listed in the product information for fluoroquinolones, although gastrointestinal symptoms are not mentioned as part of the warnings about long-lasting, disabling, or potentially irreversible ADRs.

Further assessment is required to conclude on whether updates are warranted to the current description of long-lasting, disabling, or potentially irreversible ADRs in the product information for fluoroquinolones, in terms of the potential for gastrointestinal symptoms to occur. Further assessment is required to conclude on whether regulatory action is required with regards to gastrointestinal perforation.

During patient engagement concerns were raised about the prescribing of fluoroquinolones for suspected or unconfirmed infections, particularly in urological indications such as prostatitis. In the descriptions of patient experiences provided by FQTSUK in 2019, 13 sets of comments state that the fluoroquinolone was prescribed for a suspected infection, and in 2 other sets of comments the fluoroquinolone was prescribed after a test for infection had been done but before results were available. The indication for a medicine is captured in a structured field in Yellow Card reports, but not qualifying statements such as “suspected”. The text of the 348 “Consistent” and “Potentially consistent” reports was searched for relevant terms (“suspected”, “possible”, “unconfirmed”), and reports reviewed at individual level. This identified 25 reports where the indication was stated to be a suspected infection. It is possible that this was the case for other reports, but not recorded, noting that some Yellow Card reports had unclear information (21.1%, 64/303) or no information (12.2%, 37/303) about indication. The most common suspected indications in these reports were UTI (n=7), prostatitis (n=6), epididymitis (n=3), and pelvic inflammatory disease (n=3).

4.1.2.4 Fatal outcomes

At the patient group meeting a concern was raised about the number of Yellow Card reports associated with fluoroquinolones that have a fatal outcome in the publicly available Drug Analysis Profiles on the MHRA website.

Among the 553 reports retrieved from the period between 01 January 2020 to 22 January 2023, there were 23 that reported a fatal outcome. Of these, 5 were duplicates and categorised as “Not relevant.” There were 15 reports categorised as “Not consistent,” of these 12 were reported by MAHs based on published case reports, in most of these

publications the authors did not report long-lasting, disabling, or potentially irreversible ADR associated with fluoroquinolones, or attribute the patients' deaths to ADRs suspected to be caused by fluoroquinolones (Brooker and others, 2007; Gherman-Ciolac and others, 2017; Keddie and others, 2018; Kavaliunaite and others, 2020). One case described fatal fulminant hepatitis in association with ciprofloxacin, with an onset of 2-3 days, and the patient's death 49 days after starting the course (Napier and others, 2020). The patient was reported to have previously taken ciprofloxacin without experiencing ADRs, and ADRs, other than the fulminant hepatitis, were not reported in this publication (Napier and others, 2020). There were 3 reports categorised as "Consistent," these were included in the set of 348 "Consistent" and "Potentially consistent" reports.

A further data extraction was also carried out for fatal reports, as described in section 4.1.2.4. This returned 15 reports, of which 4 were "Not relevant" as they were duplicates. There were 2 "Cannot be categorised" reports, and 7 "Not consistent" reports, these 9 reports included 4 based on case reports from the literature in which the authors did not report long-lasting, disabling, or potentially irreversible ADR associated with fluoroquinolones, or attribute the patients' deaths to ADRs suspected to be caused by fluoroquinolones (Brooker and others, 2007; Ahmed and others, 2009; Plant and others, 2018; Dwivedi and others, 2021). There was also 1 report categorised as "Consistent" and 1 categorised as "Potentially consistent," these were included in the set of 348 "Consistent" and "Potentially consistent" reports. The high proportion of Yellow Card reports with a fatal outcome that were submitted by MAHs based on literature case reports that do not describe ADRs associated with fluoroquinolones, and the extent of duplication among these reports, demonstrate that an overall figure for the number of reports with a fatal outcome cannot be taken as a reliable, without individual level review of the reports and removal of duplicates. The publicly available summaries of ADR data on the MHRA website therefore cannot be used as an accurate measure of the number of suspected ADRs reported in association with fluoroquinolones which had fatal outcomes.

The additional "Consistent" or "Potentially consistent" reports from patient engagement (n=56) did not include any with a fatal outcome.

The set of 348 "Consistent" and "Potentially consistent" reports therefore included 5 which reported a fatal outcome. Two of these 5 reports concern a patient who experienced long-lasting and/or disabling ADRs. One of these reports was submitted by an MAH in 2020 and is based on a published case report of a probable fatal interaction between ciprofloxacin and theophylline, published in 1988 (Holden, 1988). One of these reports describes a fit in a patient with epilepsy. One of these reports describes psychiatric ADRs which are listed for fluoroquinolones, with death approximately 7 months later due to pulmonary embolism. One of these reports describes a 74-year-old patient who experienced disabling and long-lasting ADRs, and died approximately 5 years later from aspiration pneumonia. It is possible that

there are other Yellow Card reports in which the patient has subsequently died, but for which this additional information is not available.

In the descriptions of patient experiences provided by FQTSUK in 2019, 3 sets of comments reported the patient's death. One of these patients received intravenous fluoroquinolones in a hospital setting to treat a chest infection. The patient experienced long-lasting and disabling ADRs and was reported to have died a in hospital approximately 2 and a half years later at the age of 75 years, with the cause being described as collapsed lungs, pneumonia and sepsis. Another one of these comments comes from an individual commenting on the prescribing of fluoroquinolones to other people. A note from FQTSUK states that a family member of this individual had died 2 months after receiving a fluoroquinolone, and experiencing unspecified problems attributed to the fluoroquinolone. This patient was stated to have a known heart problem, and the comment states "*Apparently the NHS stated he died of 'sudden adult death syndrome'."* The final comment described a patient who had received a fluoroquinolone and experienced a stiff and painful neck, approximately 6 months later the patient was admitted and readmitted to hospital within a short period with signs of an infection and sepsis and received fluoroquinolones. The patient died at the age of 88 within 24 hours of receiving a fluoroquinolone.

Patient engagement also raised a media report of an individual who died at the age of 71, stating that he had experienced ADRs associated with fluoroquinolones for the previous 6 years. The ADRs were described as being serious and long-lasting, and included neuropathy and tendon rupture. The cause of death was not stated.

Some ADRs associated with fluoroquinolones may potentially have fatal outcomes, and this is explicitly noted in the UK SmPCs. Examples include antibiotic-associated colitis, aortic aneurysm and dissection, and psychotic reactions which may include suicidal ideation. The warnings in the product information about long-lasting, disabling, or potentially irreversible ADRs do not refer to a potential for fatal outcomes. The available data from Yellow Card reports, patient experiences, and a media report do not warrant changes to this aspect of the warning about long-lasting, disabling, or potentially irreversible ADRs.

4.1.3 Drug Utilisation Study

4.1.3.1 Study design and methods

One of the outcomes of the EU referral was a Drug Utilisation Study (DUS), funded by the EMA. The purpose of the study was to collect data to investigate patterns of fluoroquinolone prescribing between 2016 and 2020. The final study report was published on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website on 01 July 2022 (Ly NF and others, 2022).

Primary objectives:

- Determine drug utilisation and prescribing patterns for fluoroquinolones between 2016 and 2020 (monthly incident use, stratified by on-label and off-label indications, and by proportion of courses discontinued early);

- Evaluate the impact of regulatory action on fluoroquinolone prescribing using time series analysis;

- Determine prescribers' compliance with warnings in the product information regarding tendinopathies and aortic dissection and aneurysm (measuring prescribing in patients at risk of these conditions and in patients with recent [30 days prior] or concomitant corticosteroid prescriptions);

- Determine prescription rates for alternative antibiotics for patients for whom systemic fluoroquinolones had previously been prescribed or discontinued.

The design was a historical population-based cohort study, using primary care data from six European countries (Belgium, France, Germany, the Netherlands, Spain, and the UK). UK data were obtained from IQVIA Medical Research Data (IMRD). Data were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). The focus of this assessment is on the UK data, as most relevant to the impact of regulatory action in the UK. Some comparisons between data from the UK and from the other countries, and trends seen in the data across all countries, are also noted.

Patients were included if they had active registration status during the study time period, plus continuous enrolment in the database for more than 12 months prior to the index date. Patients were excluded if age or sex was missing.

Incident fluoroquinolone use was defined as a recorded prescription for a fluoroquinolone in a patient with no fluoroquinolone prescription within the previous 30 days.

Early discontinuation of treatment was ascertained based on the presence of any of the following during a fluoroquinolone treatment episode: a generic treatment discontinuation code; a code suggesting lack of effectiveness; an overlapping antibiotic prescription before the end of the current treatment episode.

Indication was ascertained from codes in medical records within 14 days prior to the start date of a treatment episode (including the start date itself). If no indication was found and if another antibiotic was used in the 14 days' time window, the indication search was extended another 14 days before the other antibiotic's start date.

Indications were categorised as being either on-label or off-label. Indications that had been removed or restricted by the outcomes of the EU referral were considered off-label. For

indications where the recommendation from the EU referral was that fluoroquinolones were only indicated if the infection was severe, an algorithm was used to determine severity and therefore whether the indication was considered to be on-label or off-label. For example, a urinary tract infection (UTI) was determined to be a complicated UTI (and therefore on-label) based on a code suggestive of a UTI plus one or more of the following factors:

- genitourinary congenital anomalies;
- structural abnormalities of the urinary tract (abnormal size, raised echogenicity, hydronephrosis/hydroureter, urinary tract obstruction, ileocystoplasty);
- functional impairment of the kidneys (renal failure, vesicoureteric reflux, glomerular filtration rate less than 90 ml/min/1.73m^2);
- others (concomitant clinical conditions – diabetes mellitus, catheter associated urinary tract infection, irradiation cystitis, postoperative urinary tract infection, post renal transplantation).

This reflects the wording in the current SmPC, where some conditions are indications conditional on the suitability of other antibiotics, for example in ciprofloxacin SmPCs state that ciprofloxacin is indicated for exacerbations of chronic obstructive pulmonary disease or for uncomplicated acute cystitis *"only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections".*

The indications that were identified as on- or off-label based on a code plus use of an algorithm were: complicated urinary tract infection (on-label), complicated skin infections (on-label), recurrent cystitis in women (on-label), recurrent and non-responsive acute otitis media (on-label), and prevention of exacerbations in women with recurring urinary tract infections (off-label)

For indications where the recommendation from the EU referral was that fluoroquinolones were only indicated where other commonly recommended antibiotics are considered inappropriate (for example in acute exacerbation of chronic obstructive pulmonary disease), these were considered as off-label if the fluoroquinolone was used as first or second line, and on-label if it was used as third line (or higher). This was ascertained based on the use of at least two different antibiotics from different classes in the previous 6 days.

The authors identified risk factors for tendinitis and tendon rupture (age over 60 years, renal impairment, solid organ transplantation, prior tendon rupture or tendinitis, tobacco use) and aortic dissection and aneurysm (age over 60 years, history of other vascular aneurysms, hypertension, lipid disorder, cardiac or renal transplant, genetic conditions [Marfan's syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Turner's Syndrome],

cardiovascular syphilis, traumatic motor vehicle accident, aortic valve disorder, chronic obstructive pulmonary disease, ischaemic heart disease or cerebrovascular disease, tobacco use). These were identified by the authors as the factors consistently reported in the literature as increasing the risk of tendinitis and tendon rupture or aortic dissection and aneurysm. Concomitant or recent use of corticosteroids was defined as a prescription of a systemic corticosteroid within 30 days of fluoroquinolone exposure, including the day of fluoroquinolone start date plus one day.

Exposure to alternative antibiotics was defined as a prescription for a new antibiotic during a fluoroquinolone treatment episode, represented as a start date or an alternative antibiotic between fluoroquinolone episode start date and end date. For very serious infections (tuberculosis, pelvic inflammatory disease, moderate to severe community acquired pneumonia and complicated anthrax infection) the start of an alternative antibiotic during a fluoroquinolone treatment episode was considered to indicate the start of an additional treatment, rather than a switch in treatment.

The study calculated the number of new users of fluoroquinolones per 1,000 persons per month and stratified this measure of fluoroquinolone use by factors including age, sex, drug type (International Nonproprietary Name, INN), indications, on-label and off-label use. Stratification by route of administration was planned, but was not possible, because route was only recorded as “systemic” or “unknown”. Off-label use was presented as the ratio of off-label to on-label use. Early discontinuation proportion was expressed as the number of patients identified as stopping treatment early per 1,000 incident users per month. A time series analysis was used to analyse time points for changes in trends of prescribing; models with and without age-standardisation to the European Standard Population 2013 were used. Incident prescribing was calculated in patients with risk factors for tendinopathies, aortic dissection, or aortic aneurysm, or recent or concomitant prescribing of corticosteroids.

In each month of the study there were approximately 2.5 million to 4 million patients included from the UK. Patients could be included in more than one month of the study. The final six months of data were excluded, because patients were only considered as active until their last recorded contact with a health care professional. This would lead to a reduction in the denominator for the final months of study time, and inflation in the rates being calculated.

4.1.3.2 Drug Utilisation Study results

The incidence rates for monthly fluoroquinolone use in the UK ranged between 0.7 and 1.2 per 1,000 persons per month during the study period. After age standardisation, the upper and lower monthly incidence rates in the UK were unchanged. If the population used for the DUS had a similar age structure to the European standard population (ESP) 2013 this

would lead to there being no change or only a small change between the crude and standardised rates.

A report on the generalisability of The Health Improvement Network (THIN) databases (the previous name for IMRD-UK database) reported that demographics were similar, although there were fewer individuals aged less than 25 years in THIN compared with data from national statistics (Blak and others, 2011), and this explanation appears possible. Although it could also be possible for there to be little or no change between the crude and standardised rates even if the age distributions in IMRD-UK and the ESP 2013 differed, depending on how the incidence of fluoroquinolone use was distributed in the age groups in DUS population.

When stratified by age, over the study period the median incident fluoroquinolone use in the UK was 0.2 (range 0.2 to 0.3) per 1,000 persons per month in the under 18 years age group, 1.0 (range 0.7 to 1.2) in the 18 to 75 years age group, and 2.8 (range 1.6 to 3.4) in the over 75 years age group.

When stratified by sex monthly incident fluoroquinolone use was similar among males and females in the UK. The monthly incidence rates in terms of new users of fluoroquinolones per 1,000 people per month were not reported numerically in the DUS for the UK, but in the graphical presentation the lines for monthly incident use in males and females in the UK appear to be essentially superimposed on each other (Ly NFet al.) (page 47). This was also the case in the Netherlands, while in Belgium, France, Germany, and Spain monthly incident fluoroquinolone use was slightly higher in females than in males.

Figure 18 of the report shows the monthly incidence rates for fluoroquinolone use in the UK, stratified by on-label and off-label use. The proportion of prescriptions where the indication was unknown was very high, 84%, and therefore these rates are based on a smaller set of data than the overall and age- and sex-stratified incidence rates. The vertical blue line shows the date the DHPC concerning risk of disabling, long-lasting, and potentially irreversible side effects was distributed in the UK. The first period of SmPC implementation (in grey) is the time period during which the UK SmPCs and PILs for ciprofloxacin, ofloxacin, and levofloxacin were updated. The second period of SmPC implementation is the time period during which the UK SmPCs and PILs for moxifloxacin were updated.

The proportion of patients with early discontinuation of a fluoroquinolone ranged between 80.6 and 123.6 per every 1,000 incident fluoroquinolone users per month in the UK during the study period, without any clear temporal trends. The median rate of prescribing of alternative antibiotics in patients where fluoroquinolones have previously been prescribed or discontinued was 93.8 per every 1,000 in the UK (range 80.6 to 123.6). The range for prescribing alternative antibiotics in the UK matches exactly the range for early discontinuation of fluoroquinolones, and the was also the case in four other countries in the DUS (Germany, France, Netherlands, and Spain). In Belgium the reported ranges were

very similar (27.1 to 56.5 per 1,000 for discontinuation and 23.1 to 57.7 per 1,000 for prescribing alternative antibiotics), however the graphs depicting these monthly rates for Belgium over the study period (Ly NF and others, 2022) (pages 60 and 85) appear visually the same, and the lowest point on the graph for prescribing of alternative antibiotics is not below the 25 line on the y axis, and it is unclear whether the text or the numbers are correct. Overall, it appears that the estimates of early discontinuation were driven entirely or almost entirely by records of prescribing another antibiotic, leading to the same or very similar ranges for each of these measures. The results for early discontinuation may be an under-estimate, if some patients stopping taking a fluoroquinolone but did not have a specific code for discontinuation or for lack of treatment effectiveness recorded.

Fluoroquinolone prescribing among patients identified as being at risk of tendinitis and tendon rupture ranged between 0.5 and 0.9 per 1,000 incident fluoroquinolone users per month in the UK during the study period. Fluoroquinolone prescribing among patients identified as being at risk of aortic dissection and aneurysm ranged between 0.4 and 0.8 per 1,000 incident fluoroquinolone users per month in the UK during the study period. Fluoroquinolone prescribing among patients with concomitant or recent (within 30 days prior) prescriptions of systemic corticosteroids ranged between 0.04 and 0.1 per 1,000 incident fluoroquinolone users per month in the UK during the study period. There were no clear temporal trends over the study period in the UK data when presented graphically (Ly NF and others, 2022) (pages 80, 82, and 84), although the scale of the graphs makes visual assessment difficult.

Figure 30 of the report shows the monthly rates for incident fluoroquinolone prescriptions in the UK (all prescriptions, including those with unknown indications). Both crude and age-standardised rates are shown. The vertical blue line shows the date the DHPC concerning risk of disabling, long-lasting, and potentially irreversible side effects was distributed in the UK. The first period of SmPC implementation (in grey) is the time period during which the UK SmPCs and PILs for ciprofloxacin, ofloxacin, and levofloxacin were updated. The second period of SmPC implementation is the time period during which the UK SmPCs and PILs for moxifloxacin were updated. The red line shows a regression line fitted using joinpoint/segmented regression to identify time points where the trend in incidence rate changed. A trend of decreasing incidence of fluoroquinolone prescriptions can be seen from the end of 2018 or the beginning of 2019 onwards in the age-standardised data.

4.1.3.3 Discussion of Drug Utilisation Study results

In their discussion of the DUS results, the authors comment on the prescribing trends for fluoroquinolones in the UK during the prescribing period: *“In the UK, regression analyses suggested a decrease in prescriptions from 2019 onwards, coinciding with SmPC changes and DHPC. This timing also corresponds to EMA communications regarding fluoroquinolone restrictions (16 Oct 2018 [PRAC Recommendation], Nov 2018 [CHMP*

Opinion] and March 2019 European Commission Decision) (31,32). Prescriptions in the subset of persons stratified for on- and off-label use suggested a decrease about one year after the start of implementing SmPC changes and DHPC. The subgroup of ciprofloxacin prescriptions also showed a visually clearly appreciable reduction from 2019 onwards. Overall, most recent prescription rates were about 25% lower than baseline rates in our study. These were the most substantial reductions in prescriptions observed throughout our study. Yet this should not be attributed to regulatory interventions only, considering changes started already before." (Ly NF and others, 2022) (page 89).

The decrease in fluoroquinolone prescribing in the UK of approximately 25% between the rates the period 2016 to 2018 and the rate at the end of 2020 is consistent with usage data from England obtained from the ePACT database (see section 4.1.3.4). The author's conclusion that this decrease should not be attributed only to regulatory action is reasonable, considering the decrease in prescribing rates is observed from approximately October 2018 onwards, pre-dating the conclusion of the European review in November 2018 and communications in the UK in March 2019. The extent to which the UK regulatory action might have contributed to the duration and magnitude of this decrease in prescribing after 2019 is unknown.

As well as the total amount of fluoroquinolone prescribing, the DUS provides information about the way these medicines were prescribed. The DUS attempted to categorise the prescription by whether the indication was on-label or off-label, however there are two major limitations for this approach. Firstly, prescriptions in the UK do not necessarily contain information regarding indication. If indication was not provided in a random manner then it would not bias the estimate of the proportion of on-label and off-label prescriptions. However, if data on indication were to some extent in a systematic way related to the indication, in other words if some types of indication were more likely to be missing than others, then this would bias the estimate. The mechanism for missingness of these data, and the size and direction of any resulting bias, cannot be known from the data themselves.

Secondly, the categorisation of some indications as on-label or off-label was based on their severity, determined using an algorithm (see section 4.1.3.1). This algorithm required additional information about, for example, other medical conditions or about whether the infection was due to a resistant bacterium (for the algorithm used for identifying recurrent and non-responsive acute otitis media). For some algorithms the factors used may not have been completely aligned with UK clinical guidelines, for example the Clinical Knowledge Summary (CKS) for lower urinary tract infection (UTI) in women (Clinical Knowledge Summaries, 2023) lists a number of risks factors for complicated UTIs including virulent or atypical infecting organisms and immunosuppression, which were not included in the algorithm for complicated UTI in the DUS. Information on factors used in these algorithms may have been missing or misclassified in IMRD-UK, potentially leading to misclassification of on- or off-label status. The authors do not discuss whether these algorithms have been

validated, and do not report what overall proportion of the indications from the UK were classified as on- or off-label using the algorithms. It is therefore not possible to comment on the size and direction of any resulting bias. It should also be noted that particular concerns have been raised by patients and patient representatives about the use of fluoroquinolones for suspected infections, including in urological indications. The DUS results do not provide information about whether coded indications represent an infection confirmed by microbiological testing, or by clinical information, or whether these might represent empirical treatment on the basis of non-specific symptoms that could have had a range of possible causes, including the infection in question.

The DUS results cannot be considered to provide a reliable estimate of the proportion of off-label prescribing of fluoroquinolones in the UK.

The DUS also provided information on the rate of prescribing in patients categorised as being at risk of tendinitis and tendon rupture, or aortic dissection and aneurysm, or with concomitant or recent (within 30 days prior) prescriptions of systemic corticosteroids. Prescribing rates in these groups of patients were low. There were no clear temporal trends across the DUS period. Warnings to prescribe fluoroquinolones with caution in patients at higher risk of tendon rupture, and to avoid concomitant use of corticosteroids, were included in the UK communications in March 2019. Warnings about the risk of aortic aneurysm and dissection, were communicated to healthcare professionals in the UK via Drug Safety Update in December 2020. The DUS does not provide evidence of a change in prescribing patterns in these risk groups subsequent to the regulatory communications. There was also no clear change in the proportion of early discontinuation of fluoroquinolone prescriptions in the UK over the DUS period.

Overall, the DUS does not provide evidence of changes in the prescribing of systemic fluoroquinolones in UK primary care as a result of regulatory action in March 2019. There was no evidence that the pattern of prescribing changed after this time point, in terms of the prescribing of fluoroquinolones in specific risk groups, or the proportion of courses that were discontinued early. There was evidence of a decrease in overall usage, but as noted by the authors of the DUS, the data suggest a decrease starting before the UK regulatory action. The extent to which the UK regulatory action might have contributed to the duration and magnitude of this decrease in prescribing after 2019 is unknown.

4.1.3.4 Usage

Usage data were obtained for fluoroquinolones prescribed during the period 2018 to 2022, from the 2 databases (https://www.nhsbsa.nhs.uk/epact2), which are held by the NHS Business Services Authority (NHSBSA). ePACT2 contains data relating to the total NHS prescriptions dispensed and submitted to NHS Prescription Services by each dispenser type. The ePACT2 data is based on prescriptions prescribed and/or dispensed in the community in England. The data exclude:

- Items not dispensed, disallowed and those returned to the contractor for further clarification.

- Prescriptions prescribed and dispensed in Prisons, Hospitals and Private prescriptions.

- Items prescribed but not presented for dispensing or not submitted to NHS Prescription Services by the dispenser.

Patient identifiers were used to calculate the number of patients who received one or more prescriptions for each fluoroquinolone during each year. The same patient may have received prescriptions for more than one type of fluoroquinolone within a particular year, may have received a prescription for both a systemic and a topical fluoroquinolone within the same year, and may have received prescriptions in multiple years. Therefore, numbers of patients cannot be added across categories of type of fluoroquinolone, route of administration, or year to merge categories or create cumulative data, as this would result in some patients being counted multiple times.

These were stratified by the specific fluoroquinolone, and by route of administration – systemic or topical. The information used to generate the route of administration variable was available from the British National Formulary (BNF) product variable or was searched for specifically. However, it must be noted due to subjectivity in decision making there could be some chance of error in judgement of whether a substance was administrated topically or systemically.

Figure 1 shows the ePACT2 usage data for systemic fluoroquinolones.

Figure 1: number of patients prescribed systemic fluoroquinolones each year between 2018 and 2022 (ePACT2 data). This has been adapted into a graph by the MHRA.

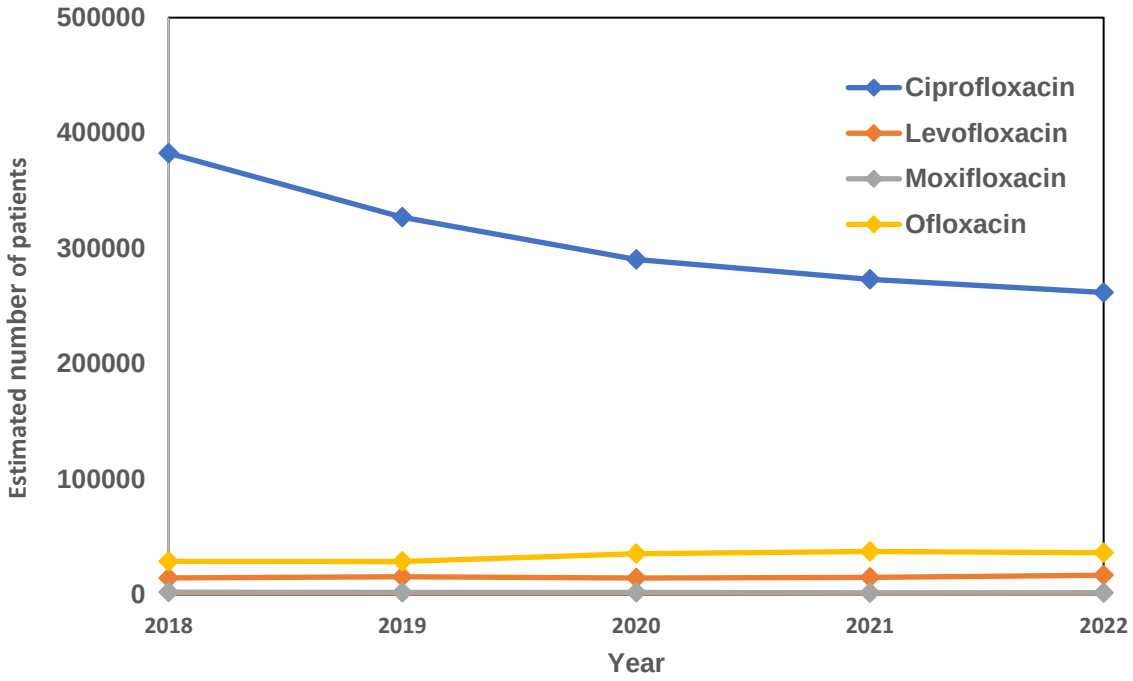
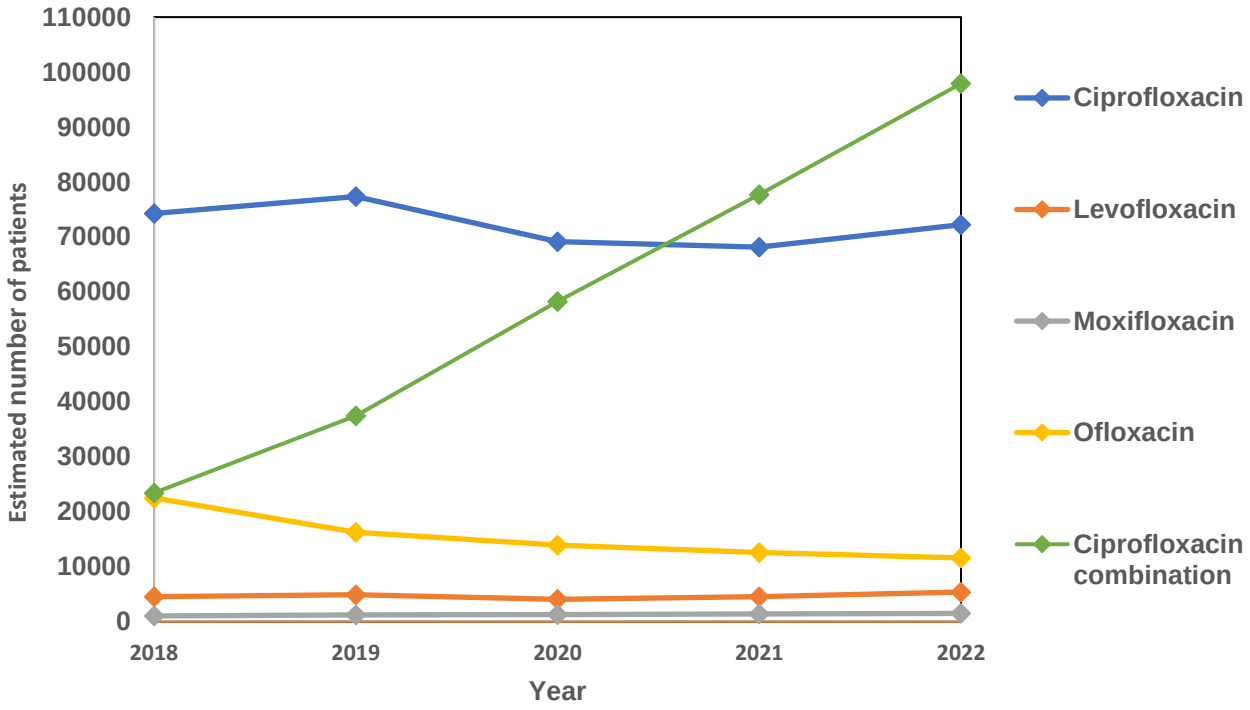


Figure 2 shows the ePACT2 usage data for topical fluoroquinolones.

Figure 2: number of patients prescribed topical fluoroquinolones each year between 2018 and 2022 (ePACT2 data). This has been adapted into a graph by the MHRA.



Ciprofloxacin was the fluoroquinolone which the greatest number of patients received, for both systemic and topical products. The number of patients who received a prescription for systemic ciprofloxacin in 2022 was 31.5% lower than in 2018 (corresponding to an absolute decrease of approximately 120,000 patients), this is comparable to the decrease in prescribing rate for all fluoroquinolones seen in the DUS over a similar time period. Use of single-constituent topical fluoroquinolones was approximately stable between 2018 and 2022 with a noticeable upward trend in the use of topical ciprofloxacin combination products over this period.

4.1.3.5 Discussion of effectiveness of risk minimisation measures

Several sources of data are available with which the effectiveness of risk minimisation for long-lasting, disabling and potentially irreversible ADRs in association with fluoroquinolone can be evaluated. These sources all have limitations, however when considered together they present a consistent picture. Prescribing of systemic fluoroquinolones in UK primary care has decreased since the UK regulatory actions associated with the risk of long-lasting, disabling and potentially irreversible ADRs in association with fluoroquinolones in March 2019, with this decrease seen in both the DUS results and in prescribing data from ePACT. There is evidence that this decline began before the regulatory action, and therefore the regulatory action did not initiate it. The extent to which the UK regulatory action might have contributed to the duration and magnitude of this decrease in prescribing after 2019 is unknown.

It is not possible to quantity the extent of awareness among UK healthcare professionals, but considering the data on prescribing, patient experiences, and Yellow Card reports it is reasonable to conclude that a proportion of the UK healthcare professionals currently involved in the prescribing of fluoroquinolones are not aware that they are associated with long-lasting, disabling, or potentially irreversible ADRs. The healthcare professionals will therefore not be able to consider these risks when prescribing fluoroquinolones, or to discuss these ADRs or signs to look out for with patients.

Fluoroquinolones continue to be prescribed in patients where the product information recommends avoiding use, for example in patients concomitantly using corticosteroids. Fluoroquinolones also continue to be prescribed for some mild to moderate infections, including urinary tract infections, and this appears to include situations where other antibiotics commonly recommended for these infections have not been understood to be inappropriate according to the criteria suggested in UK regulatory communications, such as bacterial resistance or ADRs connected to the alternative antibiotics.

It is noted that for many of the infections which are among the indications for systemic fluoroquinolones or for which fluoroquinolones have been prescribed in Yellow Card reports received by the MHRA, there are other first choice antibiotic options. For example, the NICE guidelines on antimicrobial prescribing in lower urinary tract infection (UTI) [NG109]

and recurrent UTI [NG112] do not recommend fluoroquinolones as treatment. The NICE guidelines on antimicrobial prescribing for acute pyelonephritis [NG111] and catheter-associated UTI [NG113] (with upper UTI symptoms), list four first choice antibiotics: cefalexin, co-amoxiclav, trimethoprim, and ciprofloxacin, with the note that systemic fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate. Ciprofloxacin is also listed in [NG113] as a first-choice intravenous antibiotic if the patient is vomiting, unable to take oral antibiotics or severely unwell, with a similar caveat.

Prescribing of fluoroquinolones for UTIs, apparently as the first antibiotic that has been used, is seen in Yellow Card reports, where the indication is reported as urinary tract infection (n=32); in these reports the majority either had no reference to the use of other antibiotics in otherwise detailed reports or explicitly noted that no other antibiotics had been tried (n=22), while a smaller number either mentioned at least one previous antibiotic (n=6), or had limited information and therefore in a conservative assessment it is unclear whether alternative antibiotics may have been used prior to a fluoroquinolone (n=4). In some instances, fluoroquinolones have been prescribed for suspected infections, with subsequent tests not detecting an infection.

In general, it appears patients are generally unaware of these risks at the time they are prescribed and have taken fluoroquinolones, and there are significant limitations to the current product information as a method of informing patients of these risks and allowing them to make informed choices about their treatment.

4.2 Frequency of long-lasting, disabling or potentially irreversible ADRs

The European review considered that the frequency of long-lasting, disabling and potentially irreversible ADRs in association with fluoroquinolones was *"…about 1 spontaneous case report per 10 million of DDDs (defined daily doses)"* (EMA 2018, page 20). Estimates of exposure in terms of daily defined doses are generally derived from sales data. This method for estimating a frequency for ADRs from spontaneous reports and sales data is subject to known limitations, principally under-reporting of spontaneous ADRs and any uncertainties around assumptions made about the average dose and duration of treatment. If sales data are used to estimate the denominator, then there may also be uncertainties about the proportion of product sold which is prescribed, dispensed, and taken by a patient. The European review referral assessment report concluded that *"these ADRs are most likely very rare (less than 1/10,000)[3]."* (EMA 2018, page 20). The numerator used for this calculation is not specified in this section, but earlier in the assessment report is

[3] 'Very rare' means the ADR is experienced in 1 in 10,000 patients exposed to a fluoroquinolone.

stated that *"Subsequent statistics consider only the cases 'resulting in disability' without any confounding factors (n=286)*" (EMA 2018, page 9). If the same calculation had been made using all cases from the European review resulting in disability (n=393), or even all cases resulting in disability or potentially resulting in disability (n=564), this would have increased the numerator. An approximate doubling of the numerator to 564 would presumably have resulted in an estimate of approximately 2 spontaneous case reports per 10 million of DDDs, which would likely still have been categorised as corresponding to a frequency of very rare (less than 1/10,000). The estimate of frequency category in the EMA review was therefore not sensitive to the category of cases used in the calculation but may have been sensitive to the initial search criteria, and to under-reporting.

Product information updates introduced as an outcome of the European review, and the associated regulatory communications, have referred to these ADRs as very rare. The implication is that given the calculated reporting rate of 1 spontaneous case report per 10 million defined daily doses it can be concluded with some degree of confidence that the frequency is less than 1 per 10,000, even taken into account potential under-reporting, and any limitations of the criteria used for database search in the European Review, and the process used to excluded some cases as "confounded".

The description of these ADRs as very rare has been criticised by patients and patient support groups in correspondence with the MHRA, with correspondents expressing a view that these ADRs occur more frequently than this, and that this frequency categorisation lessens the effectiveness of risk minimisation materials and communications to inform healthcare professionals of these risks.

In the descriptions of patient experiences provided by FQTSUK in 2019, 7 sets of comments note that healthcare professionals stated that the risk of ADRs was very low, or that these events are very rare.

4.2.1 UK spontaneous ADR reporting rates

The data in this review which could be used to calculate a reporting rate for UK spontaneous ADR reports have some important limitations. As discussed in section 4.2 there are important limitations to the calculation of a numerator, mainly under-reporting, the database search criteria, and the accuracy of categorisation of reports. These reports originate from the whole of the UK and may be associated with fluoroquinolones prescribed in either primary or secondary care, whereas the usage data presented in section 4.1.3.4 are for primary care prescribing in England. The usage data also have some limitations, due to the presence of prescriptions for which patient ID was is not recorded, and the presence of product for which the route of administration was not known.

Therefore, a reporting rate calculated from these data cannot in any way be treated as a reliable estimate of the proportion of patients who experience long-lasting, disabling and

potentially irreversible ADRs when prescribed a fluoroquinolone. It is interesting to note though that when such reporting rates are calculated for the different systemic fluoroquinolones for the years 2020 to 2022, they fall between approximately 2 per 10,000 and 13 per 10,000. The overall size and direction of bias from the factors affecting such a calculation noted above cannot be confidently known. But the potential for under-reporting of ADRs should be noted as likely to have a significant impact (Hazell and Shakir, 2006).

As a general point, the report-level review of Yellow Card data in section 4.1.2 also clearly shows that not all the reports received via the Yellow Card scheme in association with fluoroquinolones represent reports of long-lasting, disabling and potentially irreversible ADRs, and therefore any attempt to estimate either absolute numbers or frequency by using only summary data on the number of ADR reports associated with fluoroquinolones is not appropriate.

4.2.2 Published literature

Published literature relevant to the frequency of long-lasting, disabling and potentially irreversible ADRs in association with fluoroquinolones is limited. A study based on US claims data to evaluate disability in patients exposed to fluoroquinolones (Wilcox and others, 2020), used a primary outcome of a disability claim in combination with adverse events from two different MedDRA System Organ Classes (SOCs) from a list of 6 SOCs, with criteria around the temporality of these events. After a cohort of fluoroquinolones users was matched with an equal number of azithromycin or sulfamethoxazole / trimethoprim users by propensity scores there were 119,653 fluoroquinolones users, with 264 disability events, reported by the authors as an incidence of 0.22% (22 per 10,000). This is therefore a higher incidence than the estimate of very rare (less than 1/10,000) in the current product information. It is not known what proportion of the disability events were causally related to fluoroquinolones. The comparator group included 119,653 fluoroquinolones users, with 243 disability events, reported by the authors as an incidence of 0.20% (20 per 10,000). The adjusted odds ratio provided did not provide statistical evidence of increased odds of the outcome in fluoroquinolones users compared with azithromycin or sulfamethoxazole / trimethoprim users (adjusted OR 1.09, 95% 0.91 – 1.30). It is not known how sensitive or specific the outcome used in this study was for ascertaining cases representing the type of long-lasting, disabling and potentially irreversible ADRs described in the product information for fluoroquinolones; the authors note that the definition of disability required employment and therefore excluded the elderly and the unemployed populations. The lack of a widely accepted case definition would be a challenge for validation of the outcome used in this study. It is not known how sensitive the outcome used would be to changes in the criteria used regarding the type of the ADRs or their temporal association. It is not possible to comment with certainty on the likely size and direction of any bias introduced to the incidence estimate by misclassification of the outcome.

Materials provided by patients as part of written engagement have included references to a publication in German, produced by a health insurance organisation, Wissenschaftliches Institut der AOK (WIdO) (Schröder and others, 2020). This includes reference to an incidence of ADRs of approximately 1.2%; it appears that this publication used data from published epidemiological studies to estimate incidence rates and excess attributable risks of different ADRs associated with fluoroquinolones, for example based on published studies investigating tendinopathy outcomes (Morales and others, 2019). The estimates of incidence rates and excess attributable risks from the publication by Schröder and others would not therefore represent estimates of incidence for long-lasting, disabling and potentially irreversible ADRs.

A publication discussing multisystem ADRs in association with fluoroquinolones (Tennyson and Averch, 2016) cited an estimate of as many as 45,000 cases in the United States, based on a book published in 2015 “How We Can Halt The Cipro & Levaquin Catastrophe: The Worst Medication Disaster In U.S. History” (Cohen 2015, ISBN 1518626866); the method used to reach this estimate is not discussed by Tennyson and Averch.

4.2.3 Discussion of frequency of long-lasting, disabling, or potentially irreversible ADRs

In view of the limitations of the method used to estimate the frequency of the ADRs as “very rare” in the European review, and the potential for this description of ADRs to be counter-productive for risk minimisation, it would be appropriate to revise this in the UK product information. It appears highly probable that the actual frequency of these ADRs is higher than this very rare frequency, although the actual frequency cannot be estimated with any reliability from the available data.

It is important to note that because of the limitations associated with database search criteria and categorisation of spontaneous reports, and the unknown and potentially variable nature of under-reporting associated with spontaneous ADRs, it would not be appropriate to attempt to estimate a frequency by using the number of spontaneous reports identified in regulatory review and applying a multiplier chosen based on assumptions about the extent of under-reporting.

Since there are insufficient data to assign an SmPC frequency category to these ADRs, the only appropriate description of frequency in the SmPC would be “Not known (cannot be estimated from available data)”. In any associated regulatory communications it would be important to give some context to this change, including that while the actual frequency is not known it is likely to be greater than the previously communicated estimate of “very rare”.

It is also noted that there is some variation in the current product information in terms of the frequency categories provided for tendinopathy and tendon rupture ADRs in the SmPCs for systemic fluoroquinolones, where these ADRs are mentioned separately from long-lasting,

disabling and potentially irreversible ADRs. Published epidemiological studies are available with which the frequency of these ADRs can be estimated. It would be appropriate to consider the frequency statement for these ADRs in current product information.

4.3 Topical fluoroquinolones and long-lasting, disabling, or potentially irreversible ADRs

The previous European review included systemic fluoroquinolone products, but not topical products, given as eardrop or eyedrops. Eardrop products containing ciprofloxacin are authorised in the UK, with indications including acute otitis externa, and acute otitis media in patients with tympanostomy tubes. This includes combination products in which ciprofloxacin is combined with dexamethasone. Eyedrop products containing ciprofloxacin, levofloxacin, moxifloxacin, or moxifloxacin are authorised in the UK, with indications that include external ocular infections, treatment of corneal ulcers, superficial infections of the eye and adnexa, purulent bacterial conjunctivitis, and prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults. This includes combination products in which ciprofloxacin or levofloxacin is combined with dexamethasone.

Usage data from ePACT2 for England show that between 2018 and 2022 use of single-constituent topical fluoroquinolone products remained generally stable, while there was a clear trend for increasing use of topical ciprofloxacin combination products (see section 4.1.3.4). No use of topical levofloxacin combination products was recorded in these data in this time period.

The current UK product information for topical fluoroquinolones does not include any reference to long-lasting, disabling, or potentially irreversible ADRs. Some products include a statement that tendon ruptures have been reported with systemic fluoroquinolones, although this states that a clear association with topical products has not been demonstrated. In line with the European review conclusions on which it is based, the Drug Safety Update bulletin about the risk of long-lasting, disabling, or potentially irreversible ADRs in association with fluoroquinolones refers to systemic fluoroquinolones, specifying these as being given orally, by injection, or by inhalation.

4.3.1 Patient experiences

In written patient engagement (Annex 1) three patients expressed concerns about the potential for long-lasting, disabling, or potentially irreversible ADRs to be associated with topical fluoroquinolones. The same concern was raised by patients and patient representatives in connection with the fluoroquinolones patient group meeting.

In the patient experiences document provided by FQTSUK none of the comments explicitly related to topical fluoroquinolones. In many cases the description of the dose, route, or indication for the fluoroquinolone makes it clear that the product was a systemic fluoroquinolone.

4.3.2 UK ADR data

The set of 348 “Consistent” or “Potentially consistent” Yellow Card reports were searched for reports that had route of administration or indication that suggested a topical product. There are some infections, such as otitis media, for which both topical and oral fluoroquinolones are indicated, and therefore all reports were reviewed to confirm the route of administration. There were 4 reports where use of a topical fluoroquinolone was confirmed. All 4 reports had a patient as the initial reporter and were categorised as “Consistent.”

One report describes memory impairment, which is listed as a symptom of long-lasting, disabling, or potentially irreversible ADRs in the product information for systemic fluoroquinolones, but the duration of this ADR is not clear, it is only the dry eye syndrome and eyelid disorder which are confirmed to have lasted multiple years. Two of the reports clearly describe tendinopathies that lasted for more than 1 year. In one of these the nature and duration of the lasting effects continuing after the muscle ache resolved is not known, as no follow-up information is recorded for this report.

4.3.3 Discussion of topical fluoroquinolones and long-lasting, disabling, or potentially irreversible ADRs

The usage of topical fluoroquinolone products in the UK in primary care is likely lower than usage of systemic products. This is suggested by the ePACT2 data for England (see section 4.1.3.4) – for example, approximately 70,000 to 80,000 patients per year were prescribed a topical ciprofloxacin product in the years 2018 to 2022, while between 250,000 to 400,000 patients per year were prescribed a systemic ciprofloxacin product over the same period, with a declining trend in usage.

The difference between the number of ADR reports identified for topical products compared with systemic products is out of proportion to an approximately 4 or 5-fold difference in usage. Therefore, differences in usage are not the only reason for the different number of reports received. It is possible that there is under-reporting of ADRs associated with topical products, if the extent of under-reporting was greater for topical products than for systemic products this could contribute to the different number of reports received. It is not possible to confirm whether this is a contributory factor. It is also possible that the proportion of patients who experience ADRs meeting the search criteria used in this review is different for topical and for systemic products. The total dose and extent of systemic exposure for topical fluoroquinolones is much lower than for systemic fluoroquinolones. The SmPCs for

topical fluoroquinolone vary in their description of the extent of systemic exposure, some products state that this is *"low"* or *"negligible"*, some levofloxacin eyedrop products (see Eyflox SmPC as an example) quantify this as *"maximum plasma concentrations of levofloxacin after ocular administration are at least 1000 times lower than those reported after standard oral doses"* (SmPC states this as of time of drafting this document but may be subject to change). It is plausible that any ADRs which are dose-dependent would occur much less frequently in association with topical products, for this reason. However, long-lasting, disabling, or potentially irreversible ADRs have been reported to occur with a range of times to onset and after a range of cumulative exposures, including immediately after a single oral dose, and it is not clear how dose relates to the risk of long-lasting, disabling, or potentially irreversible ADRs at low doses. It is possible that topical products are associated with tendinopathies, and potentially other long lasting ADRs. Whether product information updates are warranted should be considered.

4.4 Psychological impacts

The product information for systemic fluoroquinolones lists a number of psychiatric events as potential ADRs, including anxiety, abnormal dreams, depression, hallucinations, psychotic reactions, and suicidal ideation. Cases of death by suicide have been reported, for example a Coroner's Regulation 28 Report from 2017 reports the death by suicide of a patient with no previous history of depression or mental health problems who had been prescribed ciprofloxacin.

In addition to these psychiatric events being listed in the product information as potential ADRs, specific psychiatric events are mentioned in the description of long-lasting, disabling, or potentially irreversible ADRs. Specifically, these ADRs are described affecting several, sometimes multiple, system organ classes and senses *"including reactions such as depression […], memory impairment, sleep disorders…"*.

4.4.1 Patient experiences

In written patient engagement (Annex 1), 12 patients expressed concerns about healthcare professionals not believing patients who report long-lasting, disabling, or potentially irreversible ADRs in association with fluoroquinolones, and being dismissive of them. The same concern was raised by patients and patient representatives in connection with the fluoroquinolones patient group meeting. In the patient experiences document provided by FQTSUK a number of the quotes mentioned psychological impacts. In at least 18 instances psychiatric ADRs are mentioned, such as insomnia, anxiety, or panic attacks – the experiences in this document are not complete accounts of all the ADRs experienced by each patient, and it is possible that other patients apart from these 18 also experienced psychiatric ADRs, such as panic attacks, insomnia, or memory impairment. In at least 12

instances impacts on psychological state or mental health that are the consequence of being worried about ADRs, or being distressed by not being believed, are mentioned. Again, it is possible that other patients apart from these 12 had similar experiences that do not appear in the quoted text.

In the online Pol.is survey provided by a patient as part of the engagement work for this review, 26 respondents responded to the statement “This condition has negatively affected my mental health.”; 84% agreed, 3% disagreed, and 11% passed (Pol.is survey). 11 respondents responded to the statement “I had/have panic attacks caused by fluoroquinolones.”; 66% agreed, 22% disagreed, and 11% passed (Pol.is survey).

Across all areas of patient engagement, many patients highlighted that they felt “gaslighted”, meaning that their experience of events was being repeatedly called into question by others. There is a strong impression that this has a serious impact on mental health for many patients affected by these ADRs.

4.4.2 UK ADR data

The set of 348 “Consistent” or “Potentially consistent” Yellow Card reports included 99 reports (28.4%) that reported at least one ADR term from the MedDRA Psychiatric disorders System Organ Class (SOC). The majority (n=90) had a patient as the original reporter, and 95 also reported at least one ADR term from another SOC. There were 232 ADR terms from the Psychiatric disorders SOC reported across these 99 reports (mean 2.3 terms per report). In total 53 different MedDRA terms were reported at the MedDRA Preferred Term (PT) level. Many of these were reported in a small number of reports; 25 of the terms appeared in only 1 or 2 reports. The MedDRA terms which appeared most frequently are summarised in table 4.

Table 4: ADRs reported in 3 or more reports from 99 Consistent and Potentially consistent Yellow Card reports that included at least one term from the Psychiatric disorders System Organ Class

MedDRA Preferred Term (PT)	Number of PTs reported	Included in current SmPC description of disabling or long-lasting ADRs? (including synonyms and related terms, and secondary events)
Anxiety	45	No (listed as an ADR separately)
Insomnia	35	Yes
Depression	29	Yes
Confusional state	11	No (listed as an ADR separately)
Nightmare	9	Yes
Panic attack	8	No
Agitation	7	No (listed as an ADR separately)

MedDRA Preferred Term (PT)	Number of PTs reported	Included in current SmPC description of disabling or long-lasting ADRs? (including synonyms and related terms, and secondary events)
Suicidal ideation	6	No (listed as an ADR separately)
Mental disorder	5	Non-specific
Restlessness	5	No (listed as an ADR separately)
Depressed mood	4	Yes
Hallucination	4	No (listed as an ADR separately)
Tearfulness	4	No
Poor quality sleep	3	Yes
Post-traumatic stress disorder	3	No
Psychotic disorder	3	No (listed as an ADR separately)
Sleep disorder	3	Yes
Stress	3	Non-specific

Some of these ADRs are already included in the description of possible symptoms of long-lasting and potentially disabling or irreversible ADRs in the product information for systemic fluoroquinolones. Some are not included in this description but are listed as potential ADRs that may be associated with the product separately from this warning about long-lasting and potentially disabling or irreversible ADRs. Some terms are not listed in the current product information; this includes some non-specific terms such as mental disorder and stress. Some of these terms may represent impacts on a patient's psychological state or mental health that are a consequence of disability and its impacts on their life, rather than having a direct biochemical or pharmacological cause, for example stress, anxiety, and tearfulness. Some, such as depression, could be caused by either or both these mechanisms.

4.4.3 Discussion of psychological impacts

It is clear that fluoroquinolones have the potential to cause psychiatric ADRs, either occurring in isolation or alongside other ADRs, and potentially occurring as part of long-lasting and potentially disabling or irreversible ADRs. It is also clear that the serious impacts that long-lasting and potentially disabling or irreversible ADRs have on the lives of patients can have impacts on their psychological state and mental health, and that this can be exacerbated when patients feel like their experience is being dismissed by healthcare professionals.

Many of the psychiatric ADRs most commonly reported in Yellow Card reports are listed as potential ADRs associated with fluoroquinolones, but only a smaller number are specifically included in the warnings about long-lasting and potentially disabling or irreversible ADRs. It would be appropriate to review the description of psychological symptoms that is included

in the product information, with a view to updating it to include terms for which there is sufficient evidence. Given the diversity of terms reported in Yellow Card reports, and the lack of widely accepted case definition for long-lasting, disabling, or potentially irreversible ADRs, it would be appropriate to use language that does not suggest psychological ADRs are strictly limited to a specific set of terms.

The psychological impacts that long-lasting and potentially disabling or irreversible ADRs may have, apart from psychiatric ADRs themselves, is outside the scope of the product information, but it would be appropriate to acknowledge this in safety communications that refer to long-lasting and potentially disabling or irreversible ADRs.

4.5 Mechanisms underlying long-lasting, disabling, or potentially irreversible ADRs in association with fluoroquinolones

4.5.1 Consideration of mechanisms in previous regulatory review

The European review included a review of non-clinical data to evaluate the potential causal relationship between the use of fluoroquinolones and long-lasting, disabling, and potentially irreversible ADRs (European Medicines Agency, 2019). The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) considered that the potential mechanisms of the ADRs would be relevant for all fluoroquinolones, as a class effect.

The European review noted that several potential mechanisms were highlighted and found to be multifactorial in a number of non-clinical studies. Oxidative stress and mitochondrial toxicity were outlined in the majority of studies and responses from MAHs that were considered as part of the European review. Other possible mechanisms included inhibition of cell proliferation and migration, reduced extracellular matrix, enhanced matrix metalloproteinase (MMP) expression, apoptosis, ischemia and chelating properties of fluoroquinolones.

4.5.2 Discussion of further data on mechanisms

The MHRA requested an MAH cumulative review of the literature relevant to the mechanism(s) underlying the disabling and potentially long-lasting or irreversible side effects that may occur in association with fluoroquinolones as a class. The request stated that this may include a summary of evidence included in the European review, but with a primary focus on any evidence not already considered in the European review, or which had become available since the European review concluded. As part of the review, the MAH was also asked to consider and provide any relevant data from nonclinical regulatory studies.

The MHRA assessment of the MAH responses identified two reviews which pre-dated the conclusion of the European review, and an *in vitro* study.

Michalak and colleagues 2017 conducted a review of "*pathobiochemical properties of fluoroquinolones"* and discussed the following mechanisms with regards to long-lasting ADRs associated with fluoroquinolone use: oxidative stress, mitochondrial dysfunction and chelation of metal ions. This review was referenced in the European review and the following comment was made. "*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."* (EMA 2019, page 20). Studies cited in Michalak and colleagues were also analysed as part of the European review.

Esposito and colleagues 2017 reviewed the neurological adverse events that may follow antibiotic administration and the mechanisms that may cause them. The review suggested that neurological ADRs linked to fluoroquinolones are mainly due to the inhibition of GABAA receptors.

Jiang and colleagues 2022 reported mitochondrial toxicity to different extents *in vitro* by the tested fluoroquinolones (trovafloxacin, levofloxacin, moxifloxacin and ciprofloxacin). The effects of both reduced mitochondrial protein levels and reduced mitochondrial DNA level were dose dependent. Of note moxifloxacin did not produce any change to mitochondrial protein or DNA levels.

Overall, the MAH concluded that there are *"no new nonclinical regulatory studies performed since the start of the Article 31 referral procedure that would add new information concerning underlying mechanisms for the potentially long-lasting, disabling, or irreversible side effects that may occur in association with the use of ciprofloxacin or moxifloxacin".*

In addition to these publications, as part of written patient engagement the MHRA was made aware of an article (at the time not peer-reviewed) which addresses the possibility that a long-lasting fluoroquinolone metabolite may be the cause of the disabling and potentially long-lasting or irreversible ADRs (Dalton, 2021). The author acknowledges that further studies are needed to isolate and identify fluoroquinolone metabolites in ADR patients and correlate these with serious side-effects.

It is not possible to make conclusions about potential mechanism(s) that could be used to inform risk minimisation for disabling and potentially long-lasting or irreversible side effects associated with fluoroquinolones.

4.6 Potential for increased risks relating to long-lasting, disabling, or potentially irreversible ADRs when NSAIDs are used concurrently or subsequently

4.6.1 Patient experiences

In the descriptions of patient experiences provided by FQTSUK in 2019, 5 sets of comments refer to non-steroidal anti-inflammatory drugs (NSAIDs). In three comments, the potential for NSAIDs to increase risks or to exacerbate ADRs is mentioned, but the comment does not state that the patient personally took NSAIDs or experienced these effects. In two comments the patient stated that they had taken unspecified NSAIDs after they began to experience long-lasting, disabling, or potentially irreversible ADRs in association with a fluoroquinolone, and stated that their symptoms became worse after taking the NSAID. These experiences also include instances where patients reported that their symptoms worsened after taking medicines from other classes, not including steroids (one comment), or in some cases in association with food and drink (one comment). Similar experiences have been reported in some Yellow Card reports.

The product information for some systemic fluoroquinolone products contains a warning that seizures threshold may be lowered when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold. There are case reports of such events occurring, for example the fatal case report cited in section 4.1.2.4 (Holden, 1988). These risks are distinct from any potential risk of NSAIDs increasing the occurrence or severity of that long-lasting, disabling, or potentially irreversible ADRs.

4.6.2 UK ADR data

The set of 348 reports that were “Consistent” or “Potentially consistent” with a disabling or long-lasting ADR Yellow Card reports included 46 (13.2%) where concomitant or subsequent use of an NSAID was recorded as a co-suspect or concomitant medicine or was mentioned in the report narrative (based on a search for the terms aspirin, naproxen, ibuprofen, diclofenac, NSAID, non-steroidal, and non-steroidal). The reports were reviewed and categorised according to the following 3 categories:

Table 6: Categorisation of 46 reports with use of NSAIDs, or NSAIDs mentioned in the narrative

Category	Description	Number of reports
1	No information given about whether NSAIDs were suspected to have contributed to the ADRs occurring, or worsened ADR symptoms	40

Category	Description	Number of reports
2	Reporter refers to NSAIDs being known to increase risk or worsen ADRs, but this is not stated to have happened in this patient	2
3	Confirmation that NSAIDs were suspected to have increased risk or worsened ADRs in this patient	4

Of the 46 reports, for a majority of the reports 40 (87%) there was no information provided in the narrative to indicate whether the NSAIDs were suspected to have contributed to the ADRs occurring, or whether the NSAID caused the symptoms to worsen in these specific cases. Also, the reporter did not comment on the NSAID as a possible risk factor. In 2 (4.3%) reports, the reporter suggests that NSAIDs should not be used alongside fluoroquinolones or that they worsen the ADRs. However, it was not possible to judge whether the NSAIDs increased the risk or worsened the ADR so it is not known whether the ADRs would have been different if the NSAIDs had not be used. For 4 reports (8.7%) there were details given in the narrative that confirm that the ADRs were suspected to have worsened or were exacerbated as a result of NSAID use. Just under half of the reports were reported directly by patients (n=20), 43.5%. Of the 46 reports, 30 (65.2%) were male patients, this may be due to usage patterns in primary care and is generally consistent with the proportion of male patients in the set of 348 “Consistent” or “Potentially consistent” reports (55.3%, 189/342 were male in reports with known sex).

Discussion

Of the 46 reports that were identified as mentioning concomitant or subsequent use of an NSAID, for a majority of reports (87%), there was no information provided to indicate whether the NSAIDs were suspected to have contributed to the ADRs occurring or whether they caused the symptoms to worsen. It was not always possible to be certain about the reporter’s views about whether the risk was present.

4.6.3 Published literature

The possibility of interactions between NSAIDs and fluoroquinolones was not discussed in detail by the European review. It was however acknowledged that drug interactions between NSAIDs, theophylline, caffeine and ciprofloxacin have been identified as important factors in toxicity (EMA, 2019). It was also acknowledged that there are data that show that co-administration of the NSAID fenbufen enhances the binding of quinolones to GABA receptors leading to clinically significant symptoms.

The MHRA requested an MAH cumulative review of the literature and data from non-clinical regulatory studies relevant to possible interactions between fluoroquinolones as a class and NSAIDs. The MAH provided the results of a literature search, and their conclusion that no pattern of ADRs, except seizure, in drug-drug interactions between NSAIDs and quinolones

could be identified. The MAH also noted that they had performed non-clinical studies concerning possible interactions between fluoroquinolone antibiotics with NSAIDs. The MAH stated that studies that included ciprofloxacin and other quinolones (but not moxifloxacin) indicated that generally acute toxic interactions depend on the type of both the NSAID and the gyrase inhibitor, and that the interval between administration of the quinolone and the NSAID was also a factor.

A search of the literature was performed by the MHRA. This demonstrated that much of the literature in this area is over 20 years old and investigates the convulsive effects reported after co-administration of fluoroquinolones and NSAIDs. The evidence reviewed suggests an inhibitory effect on GABA receptors as a result of interaction between certain NSAIDs and fluoroquinolones. Much of the literature appears to investigate the effects of the NSAID fenbufen and its metabolite biphenyl acetic acid (BPAA). However, fenbufen is not authorised in the UK and evidence reviewed thus far does not indicate that this metabolite is available following administration of other NSAIDs. Much of the data reviewed is from *in vitro* studies and the relevance of the concentrations used when compared to clinical exposures is not clear. A summary of literature reviewed is provided below. Lastly, owing to the age of these publications, many of the investigated fluoroquinolones are no longer available on the UK market.

Hori and colleagues 1989 reported that new quinolones inhibited GABA-receptor binding in a concentration dependent manner *in vitro*. Flurbiprofen enhanced the inhibitory effect of all new quinolones tested (ciprofloxacin, fleroxacin, norfloxacin, enoxacin and ofloxacin) except fleroxacin. Indomethacin decreased the binding of norfloxacin, enoxacin and ofloxacin but aspirin did not affect the inhibitory activities of new quinolones. Halliwell and colleagues 1991 demonstrated that the inhibitory action of ciprofloxacin *in vitro* was enhanced in the presence of 100µm fenbufen by approximately five-fold whereas the antagonism of GABA responses by ofloxacin was unaffected. BPAA (100µm) had a dramatic effect on the inhibitory action of both ciprofloxacin and ofloxacin. The authors noted that the mechanism of this interaction is not known.

Kawakami and colleagues 1993 reported that the GABA response was inhibited by enoxacin in a dose-dependent manner. The inhibitory effect of enoxacin was 80-fold potentiated in the presence of 10 microM felbinac. The GABAA-antagonistic interaction between these two drugs *in vitro* was considered a possible mechanism of convulsant reaction after concomitant administration of new quinolone antibacterial agents and NSAIDs *in vivo*. Yakushiji and others 1992 demonstrated *in vitro* that co-administration of new quinolones and some NSAIDs resulted in a marked suppression of the GABA response. This was dependent on the concentration of either the new quinolone or the NSAID tested. The inhibitory potency of new quinolones in combination with BPAA was ranked in order, norfloxacin > enoxacin > ciprofloxacin > ofloxacin, and that of NSAIDs in combination with enoxacin was BPAA > indomethacin = ketoprofen > naproxen > ibuprofen > pranoprofen.

Diclofenac, piroxicam and acetaminophen did not affect GABA responses in the presence of enoxacin.

4.6.4 Discussion of risks associated with concurrent of subsequent use of NSAIDs

Data from patient experiences and spontaneous reports are limited with regards to the potential for concurrent or subsequent use of NSAIDs to increase the risk that long-lasting, disabling, or potentially irreversible ADRs may occur, to increase the severity of these ADRs, or to cause these ADRs to worsen at a later date. These data are insufficient to warrant updates to the product information. And it is noted that some patients have reported exacerbation of their symptoms in connection with medicines from other classes, as well as some foods and drinks in some reports. It is possible that some of these associations may have occurred by chance, but if multiple different types of medicines can cause exacerbation of symptoms a warning focussing on NSAIDs only would be potentially misleading.

Effects on GABA receptors by fluoroquinolones and NSAIDs or their metabolites provide a potential mechanism for pharmacodynamic interactions that might produce ADRs which result from GABA antagonism. But it is not clear that this provides sufficient evidence to conclude that long-lasting, disabling, or potentially irreversible ADRs, including ADRs affecting tendons and other body systems, are more likely to occur with the concurrent use of fluoroquinolones and NSAIDs, or that this provides a mechanism for worsening of these symptoms if an NSAID is subsequently taken. It should also be noted that some of these non-clinical data related to fenbufen and its metabolite phenylacetic acid. Fenbufen is not authorised in the UK, and data from fenbufen and phenylacetic acid cannot necessarily be extrapolated to all NSAIDs.

4.7 Overall discussion and conclusions

A causal association between fluoroquinolones and long-lasting, disabling, or potentially irreversible ADRs was established in the previous European review. There is evidence that new patients have continued to be affected by these ADRs since the previous regulatory action in the UK, and that some UK healthcare professionals continue to be unaware of these risks.

Risk factors have been identified for some ADRs associated with fluoroquinolones, such as concomitant use of corticosteroids which is known to increase the risk of tendinopathies. These risk factors may have an impact on the occurrence and severity of these ADRs when they appear as part of long-lasting, disabling, or potentially irreversible ADRs. For example if a patient experiences long-lasting, disabling, or potentially irreversible ADRs associated with a fluoroquinolone and is also taking concomitant corticosteroids this might be expected

to increase the chance of a tendon rupture occurring as part of the associated tendinopathies. But for other factors that have been suggested to specifically increase the risk of long-lasting, disabling, or potentially irreversible ADRs, evidence to confirm such an association is generally limited. It is also clear that long-lasting, disabling, or potentially irreversible ADRs can occur in patients regardless of known or hypothesised risk factors for ADRs associated with fluoroquinolones. It is not possible to identify a group of patients where the risk of long-lasting, disabling, or potentially irreversible ADRs in association with fluoroquinolones is not present, and not possible to adequately minimise the risk of these ADRs occurring solely with restrictions based on known or hypothesised risk factors. Therefore, reducing the number of patients in the UK each year who are affected by long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones would require reducing the number of patients exposed to fluoroquinolones, by limiting the use of fluoroquinolones to situations where their use is necessary and where the potential benefits for patients are great enough to outweigh the risks. Successful measures to reduce this risk would result in reductions in use of fluoroquinolones with continuing use in situations where this is necessary (for example because of pathogen susceptibility, resistance to other antibiotics, or other antibiotics being ineffective, contraindicated or not tolerated), and with patients able to make informed choices about their treatment.

At the time of the review, regulatory information described these ADRs as “very rare” (less than 1 per 10,000). The method used to calculate this frequency has substantial limitations. The proportion of patients who take a fluoroquinolone who will be affected by long-lasting, disabling, or potentially irreversible ADRs cannot be estimated with confidence, but is likely to be greater than the previously communicated estimate of “very rare”. Description of the frequency as “very rare” may be counter-productive for messages about risk minimisation. While the frequency cannot be estimated precisely using available data, the updated reporting incidence indicates a minimum frequency of between 1 and 10 per 10,000. The frequencies of tendinopathies were also inconsistent across the product information for systemic fluoroquinolones, at the time of the review, and in some cases frequencies were presented in the product information which were lower than those suggested by available epidemiological data.

The majority of the data on the risk of long-lasting, disabling, or potentially irreversible ADRs relate to systemic products. Data are much more limited for topical products, although reports of long-lasting tendinopathies in association with topical fluoroquinolones have been received.

It is clear that fluoroquinolones have the potential to cause psychiatric ADRs, either occurring in isolation or alongside other ADRs, and potentially occurring as part of long-lasting and potentially disabling or irreversible ADRs. The CHM considered that further review of possible psychiatric symptoms, with a view to updating the product information if warranted would be appropriate, in which case it would be appropriate to use language that

does not suggest psychological ADRs are strictly limited to a specific set of terms. The psychological impacts that long-lasting and potentially disabling or irreversible ADRs may have, apart from psychiatric ADRs themselves, is outside the scope of the product information, but it would be appropriate to acknowledge this in any safety communications associated with long-lasting and potentially disabling or irreversible ADRs.

Several mechanisms have been proposed as potentially underlying long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones, and non-clinical studies have been conducted to investigate these. A complete cumulative review of the currently available literature is required in order to reach conclusions about the strength of evidence to support particular mechanisms as underlying these ADRs in a clinical context, or to identify any important areas of uncertainty regarding mechanisms.

Current data on the potential for concurrent or subsequent use of NSAIDs to increase the risk that long-lasting, disabling, or potentially irreversible ADRs may occur, increase the severity of these ADRs, or cause them to flare or worsen at a later date are insufficient to warrant updates to the product information. It would be appropriate to continue to monitor any clinical evidence for such interactions, for example from the Yellow Card scheme.

5. CHM advice

At the meeting of the CHM on 6 May 2023 the following advice was sought:

The CHM were reminded of the previous regulatory actions taken in association with this risk in the UK in 2019, which included a DHPC, and Drug Safety Update article, introduction of a patient sheet to help healthcare professionals advise patients, and a communication sent via the Central Alerting System.

The CHM were presented with a paper reviewing the effectiveness of existing measures to minimise the risk of disabling and potentially long-lasting or irreversible side effects associated with fluoroquinolones. The views of patients were included in the review, these were received by the MHRA in writing and at a meeting held with a group of patients and patient representatives. Data considered in the review included patient experiences, spontaneous ADR data from the Yellow Card scheme, the results of a Drug Utilisation Study, primary care prescribing data, and data from the scientific literature.

The CHM also heard directly from patients and patient representatives about their experiences of side effects associated with fluoroquinolones and heard feedback from the Pharmacovigilance Expert Advisory Group.

The CHM noted that there are multiple factors that will contribute to risk minimisation for this issue, and that both regulatory action and action in UK healthcare systems more widely are needed. The CHM considered that any regulatory actions should be proportionate, and that there are some patients seen in primary care for whom fluoroquinolones are an appropriate treatment option.

The CHM discussed a range of possible options to further minimise this risk for inhaled and systemic fluoroquinolones. The CHM considered that it would be appropriate to strengthen warnings in the product information, such that systemic fluoroquinolones must not be used if other appropriate options are available. The CHM also supported revision of the description and the frequency statement for these events in line with available data. The CHM did not consider that there was sufficient evidence to warrant additional regulatory action for topical products at this time.

The CHM supported regulatory communications to remind UK healthcare professionals about this risk and the existing risk minimisation measures, and any additional UK regulatory action taken by the MHRA. The CHM advised the MHRA to consider how routes for communication in addition to regulatory could maximise distribution of these safety messages, for example publications aimed at healthcare professionals. To increase the reach of safety communications by the regulator the CHM recommended working in partnership with relevant organisations with an interest in optimising the use of

fluoroquinolones so they are used in scenarios where the balance of benefits and risks is most favourable. The CHM also advised that the MHRA should liaise with appropriate stakeholders to explore whether additional alerts about the risk of potentially long-lasting or irreversible side effects associated with fluoroquinolones could be introduced in electronic prescribing systems.

Other regulatory actions to minimise risk, including a patient alert card, restriction of the clinical setting in which fluoroquinolones are used, written documentation of informed consent, or restriction of fluoroquinolones to life-threatening situations only, were not considered appropriate at this time by the CHM, based on their feasibility, likely effectiveness, and the potential for adverse impacts on the UK healthcare system.

The CHM considered that, in addition to actions that are part of the MHRA's regulatory remit, more scientific research is needed, including into the mechanisms by which fluoroquinolones cause these events and to develop a case definition for disabling and potentially long-lasting or irreversible side effects associated with fluoroquinolones.

6. Next steps

Action Undertaken as of August 2024

Since conclusion of the CHM review, the MHRA has been working to enact the recommendations.

- The product information for fluoroquinolones has been updated to state that they should only be used when other commonly recommended antibiotics are inappropriate.

- The description of disabling and potentially long-lasting or irreversible side effects in the safety information has been updated, to include more detail about the range of psychiatric symptoms that may occur as part of these reactions. These may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion or depression.

- Description of these disabling and potentially long-lasting or irreversible side effects has been moved from ‘very rare’ to the first bullet point in the ‘rare’ category in the Patient Information Leaflet (PIL).

- A Drug Safety Update to remind healthcare professionals about the risks was published in August 2023 and a Drug Safety Update covering psychiatric side effects specifically was published in September 2023.

- To communicate the additional regulatory action, a Drug Safety Update was published in January 2024 and distributed through healthcare professional subscriber channels.

- The January Drug Safety Update was published alongside a Press Release which was pitched to healthcare professional publications as well as national media to raise awareness.

- Since the findings of the review were released, the MHRA has been working with UK Healthcare Organisations such as The National Institute for Health and Care Excellence (NICE), British Infection Association (BIA) and UK Health Security Agency (UKHSA) to ensure relevant guidelines and advice is updated in accordance with the recommendations and to promote key safety messages.

Next steps

The MHRA will continue to work with healthcare professional organisations on the additional recommendations.

The MHRA will also work towards the CHM's recommendation to liaise with appropriate stakeholders to explore whether additional alerts about the risk of potentially long-lasting or irreversible side effects associated with fluoroquinolones could be introduced to electronic prescribing systems used by healthcare professionals.

The MHRA will continue to monitor the safety of fluoroquinolones and will take further regulatory action if this is appropriate.

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8. Glossary of terms

Adverse drug reaction
A suspected side effect of a medicine.

Agence nationale de sécurité du médicament et des produits de santé (ANSM)
Responsible for assessing the benefits and risks associated with the use drugs and other medical products throughout their life cycle in France.

Clinical data or clinical studies
Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

Clinical trial
A research study that tests the effectiveness and safety of medicines in humans.

Concomitant medication
A medication that someone is taking that is not the medicine under investigation.

Cohort study
In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between 2 groups, and usually accompany ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between 2 groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Contra-indicated/Contraindication
When a drug should not be used in a specific situation, condition, or group of people because it may be harmful to the person.

Cumulative review

Drug Utilisation Study (DUS)
Drug utilisation studies investigate how medicines are prescribed, dispensed and/or used in everyday clinical practice.

Epidemiological studies
Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

EudraVigilance
EudraVigilance is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network.

European Medicines Agency (EMA)
The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

Food and Drug Administration (FDA)
Federal agency responsible for regulating and overseeing the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food, cosmetics, products that emit radiation and tobacco products in the USA.

Hazard ratio
One measure of risk. Hazard ratios estimate the risk for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk.

Healthcare databases
Healthcare databases are systems into which healthcare providers routinely enter clinical and laboratory data during usual practice as a record of the patient’s care.

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Marketing authorisation holder
The company or other legal entity that has the authorisation to market a medicine in the UK.

Medical Dictionary for Regulatory Activities (MedDRA)
The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices.

Meta-analysis

A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Non-clinical or pre-clinical studies
In drug development, preclinical development, also named preclinical studies and non-clinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected.

Observational study
A type of research study where data on health outcomes are collected and analysed, without changing what treatments or procedures people receive.

Odds ratio
A measure of risk for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk.

Off-label
Relating to the prescription of a medicine for a condition which it is not officially licensed for.

Null Hypothesis / Null
The theory or hypothesis that an observed difference is due to chance alone and not due to a systematic cause.

Patient Information Leaflet
Medicine packs includes a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Periodic safety update report (PSUR)
These are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorisation.

Pharmacodynamics
Pharmacodynamics describes the effects a medicine has on the body.

Pharmacokinetics
Pharmacokinetics describes how the human body affects a medicine, such as , how the medicine is absorbed, chemical changes the medicine undergoes, how the medicine moves through the body and is eventually removed from the body.

Pharmacovigilance Risk Assessment Committee (PRAC)

Committee that assesses and monitors the safety of human medicines in Europe.

Poisson regression
Poisson regression is a statistical method that attempts to determine the strength and character of the relationship between one dependent variable and a series of other variables.

Prevalence
The proportion of individuals in a defined population that have a disease or other health outcomes of interest at either a specified point in time (known as point prevalence) or during a specified period of time (period prevalence).

Primary Care
Primary care services provide the first point of contact in the healthcare system, acting as the ‘front door’ of the NHS. Primary care includes general practice, community pharmacy, dental, and optometry (eye health) services.

Prophylaxis
Treatment given or action taken to prevent disease.

Randomised controlled clinical trial
A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention.

Regression analysis
Regression is a statistical method that attempts to determine the strength and character of the relationship between one dependent variable and a series of other variables.

Retrospective study
A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

Risk factor
A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Secondary Care
Secondary care services are those provided by medical specialists, who in general do not have the first contact with the patient.

Self-controlled case series
A type of study where health outcomes are compared for each study participant in the time before they are exposed to some event (such as taking a medicine) and in the time after they are exposed to it. This is a way of being able to measure the effects of the exposure in a way that is not affected by other factors (like whether a person has a certain genetic makeup) because these stay the same for each person before and after the exposure.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Systematic review
A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

Systemic
Relating to the whole of the body. Systemic medicines are taken by mouth or as an injection.

Tendinitis
Inflammation of a tendon.

Tendinopathies
Tendinopathies are conditions affecting the tendons, which connect muscles to bones. Symptoms can include pain, swelling, and stiffness, which may affect movement.

Time series analysis
A method of analysing data that have been collected over a period of time. It can be used to understand changes or patterns occruing over time.

Topical
Relating or applied directly to a part of the body.

UK Health Security Agency (UKHSA)
The UK Health Security Agency (UKHSA) is responsible for protecting the UK public from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Yellow Card scheme
The MHRA's scheme for healthcare professionals and members of the public to report suspected adverse reactions for a medicine or vaccine, as well as medical devices and other products.

9. Annexes

Annex 1 – Themes from written patient engagement

Annex 2 – Themes from the fluoroquinolone patient group meeting

Annex 1– Themes from written patient engagement

Themes from 53 sets of written comments from patients and patient representatives. The number of comments raising each theme are noted, as are some commonly raised specific aspects within each theme. Each set of written comments could raise more than one theme, and so the numbers of comments and of specific aspects will sum to more than 53.

Theme	Specific aspects
Healthcare professionals (HCPs) are not aware of the risks of fluoroquinolones (n=37)	HCPs do not believe patients who report adverse reactions (ADRs) and are dismissive of them (n=12); Specific suggestions made (n=9); these included automated alerts at time of prescribing, including information as part of medical training, and writing to HCPs
The use of fluoroquinolones should be further restricted (n=30)	Concerns about the use of fluoroquinolones for suspected infections, or without test results to confirm an infection (n=10); fluoroquinolones should only be used in hospitals / should not be prescribed by GPs (n=10); fluoroquinolones should be used for life-threatening infections only (n=8); fluoroquinolones should be withdrawn (n=2)
Comments about clinical practice (n=22)	Treatment for these ADRs is lacking (n=10); recognition and support within the NHS is lacking (n=7); cost impact of these ADRs for the NHS (n=3)
More needs to be done to make patients aware of the risks of fluoroquinolones (n=21)	Informed consent should be obtained when prescribing (n=11); the patient information leaflet should be updated (n=4); warnings about risks should be placed on the boxes (n=3)
There is a need for a recognised diagnosis and/or medical code for long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones (n=11)	–

Specific groups of people or risk factors may increase risk of ADRs, or exacerbate these ADRs (n=10)	Suggested factors that may increase risk: • Athletic background; • Collagen disorders including hypermobility spectrum disorder; • Mitochondrial conditions; • Myalgic encephalomyelitis/chronic fatigue syndrome; • Renal impairment; • Concurrent use of NSAIDs; • Steroids; • Subsequent use of other antibiotics; • Dental products containing fluorine; • Certain foods and drinks (highly processed food, sugar, caffeine, alcoholic spirits specifically mentioned).
Long-lasting, disabling, or potentially irreversible ADRs associated with fluoroquinolones may be under-reported or more frequent than described in current regulatory information (n=9)	–
Providing data (n=5)	• Results from a Pol.is survey; Publication by Pieper 2021; • Unpublished non-clinical article; • SFPT communication; • Media coverage in France.
Concern about the potential for risks to be associated with topical fluoroquinolone products (n=3)	–
Concerns about Yellow Card reporting or awareness of the Yellow Card Scheme (n=2)	–

Other (n=5)	• Patients are often misdiagnosed. Concerns about possible sexual or reproductive risks; • Suggests review of risks of COVID-19 vaccines in patients with these ADRs; Suggests testing of affected patients (not specified); • Suggests surveying HCPs about their understanding of prescribing guidelines; • Concerns about fluoroquinolones in the food chain;

Annex 2 – Themes from the fluoroquinolones patient group meeting

Theme	Specific aspects
Healthcare professional (HCP) awareness about disabling and long-lasting or irreversible harms associated with fluoroquinolones	• Healthcare professionals do not easily recognise these adverse reactions (ADRs); • If HCPs do not see these ADRs, or understand how they can occur, they will not have a high level of concern about them; • Patients often have a strong sense they are not believed by HCPs.
Measures to minimise risks	• Concerns were raised about the way fluoroquinolones are used in the UK, and about the effectiveness of current measures to minimise risks; • Suggestions were made for some specific actions that could be taken to minimise these risks, for example that fluoroquinolones should not be prescribed in primary care; • The cost to the NHS associated with these ADRs.
Mechanisms	• Effects on mitochondria, gamma-aminobutyric acid (GABA) receptors, and vagal tone were mentioned as mechanisms • Concerns were raised about the level of detail about mechanisms and the prominence given to this information in regulatory information and communications
Nature of ADRs caused by fluoroquinolones;	• Variable time to onset of the ADRs; • ADR reporting summaries on the MHRA website include reports with a fatal outcome;

factors that increase risk	• Potential additional risk factors (e.g. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, hypermobility or Ehler-Danlos Syndrome, or older adults; • Gastrointestinal ADRs may occur; • Other medicines (including but not limited to NSAIDs) may increase risks or exacerbate ADR symptoms;
Psychological impacts	• A high proportion of affected patients experience report psychological effects; • As well as psychological ADRs, patients' mental health may be affected by their experiences, including not being believed by HCPs
Terminology used to describe "disabling and potentially longlasting or irreversible side effects"	• The importance of having a recognised diagnosis, and associated medical codes (e.g. Read codes), was raised.
Under-reporting of ADRs; issues with the Yellow Card Scheme	• Concerns that these ADRs are under-reported; Concerns about the Yellow Card Scheme is not well known enough, or being promoted sufficiently; • Concerns about the usability of the Yellow Card website.
Lack of available treatments	• There is a lack of treatment options for these ADRs
Specific information mentioned	• Publications (Freeman et al. 2021; Golomb et al. 2015; • Michalak et al. 2017; Pieper 2021) • Online articles, including recent publications in France by • ANSM and the SFPT; • Coroner's Preventing Future Deaths letter; • Patient testimonies and experiences