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Systemic and inhaled fluoroquinolone antibiotics – reminder on restrictions of use

Dear Healthcare Professional,

A. Menarini - Industrie Farmaceutiche Riunite - S.r.l., Anfarm Hellas S.A., Azure Pharmaceuticals Ltd., Bayer Ltd., Clonmel Healthcare Ltd., Cooper Pharmaceuticals S.A., Delorbis Pharmaceuticals Ltd., Farmarosib S.r.l., Fresenius Kabi Italia S.r.l., Ibigen S.r.l., JV Healthcare Ltd., Medochemie Ltd., Neofarma Pharmaceuticals Ltd., NM Pharma Ltd., Noridem Enterprises Ltd., Norma Hellas S.A., Piam Farmaceutici, Remedica Ltd., Rowex, Sanofi S.r.l., TAD Pharma GmbH, in agreement with the European Medicines Agency (EMA) and the Malta Medicines Authority, would like to remind you of the following:

Summary

- Recent study data suggest that fluoroquinolones continue to be prescribed outside of the recommended uses.
- Systemic and inhaled fluoroquinolones should **NOT** be prescribed for:
    - patients who have previously had serious adverse reactions with a quinolone or fluoroquinolone antibiotic;
    - non-severe or self-limiting infections (such as pharyngitis, tonsillitis and acute bronchitis);
    - mild to moderate infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease (COPD), acute bacterial rhinosinusitis and acute otitis media) unless other antibiotics that are commonly recommended for these infections are considered inappropriate;
    - non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
    - preventing travellers' diarrhoea or recurrent lower urinary tract infections.
- Systemic and inhaled fluoroquinolones are associated with very rare, serious, disabling, long-lasting and potentially irreversible adverse reactions. These products should be prescribed only for approved indications and after careful assessment of the benefits and risks in the individual patient.

Background to safety concern

The European Medicines Agency (EMA) made strong recommendations to restrict the use of systemic and inhaled fluoroquinolones following an EU-wide review conducted in 2018 to evaluate the risk of serious and long-lasting (lasting months or years), disabling and potentially irreversible adverse reactions mainly affecting the musculoskeletal and nervous system. As a consequence of the review conducted by EMA, the use of fluoroquinolone medicines was significantly restricted in 2019.

These serious adverse reactions can include tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, hallucinations, psychosis, sleep disorders and impaired senses (hearing, vision, taste and smell). Tendon damage (especially to Achilles tendon but other tendons can also be involved) can occur within 48 hours of commencing treatment or the effects can be delayed for several months after stopping treatment.

An EMA-funded study was carried out ("Impact of European Union Label Changes for Fluoroquinolone Containing Medicinal Products for Systemic and Inhalation Use" (EUPAS37856)) which was based on an analysis

of prescribing rates for fluoroquinolones in six European healthcare databases (from Belgium, France, Germany, the Netherlands, Spain and the United Kingdom).

The study suggests that fluoroquinolones may still be used outside the authorised indications. However, due to the limitations of the study no definitive conclusions can be drawn.

- **Healthcare professionals** are reminded to advise patients:
  - of the risk of these serious adverse reactions;
  - of the potential long-lasting and serious nature of these effects;
  - to immediately seek a physician at the first signs of these serious adverse reactions prior to continuing treatment

- **Special caution** should be taken in patients who concurrently are treated with corticosteroids, in elderly, patients with renal impairment and patients who have undergone solid organ transplants, as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated in these patients.

Further information

For more details, please refer to the EMA review at:
https://www.ema.europa.eu/en/news/fluoroquinolone-antibiotics-reminder-measures-reduce-risk-long-lasting-disabling-potentially

Call for reporting

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system Adverse Drug Reactions (ADRs). Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Malta Medicines Authority Post-licensing, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, or sent by email to: postlicensing.medicinesauthority@gov.mt. Please report the product name and relevant details.

Adverse events should also be reported:
Company contact point

Company	Product name	Email	Phone
A. Menarini - Industrie Farmaceutiche Riunite - S.r.l.	Quofenix (delafloxacin)	pv@ammangion.com	+356 2397 6000
Anfarm Hellas S.A.	Moxifloxacin Anfarm 400mg/250ml solution for infusion (moxifloxacin hydrochloride 400/250 mg/ml)	phvigilance@anfarm.com alex.fenech@europharma.com.mt	+302 106831632, +306 932331620, +356 23859239
Azure Pharmaceuticals Ltd.	Ciplox 500 mg film-coated tablets (ciprofloxacin 500mg)	chiara.bilocca@azure-pharma.com	+356 99447352
Bayer Ltd.	Avelox (moxifloxacin) solution for infusion 400mg/250ml Ciproxin (ciprofloxacin) 500mg film-coated tablets	pv@alfredgera.com	+356 99474162
Clonmel Healthcare Ltd.	Profloxin 250 mg film-coated tablets (Ciprofloxacin 250mg), Profloxin 500 mg film-coated tablets (Ciprofloxacin 500mg)	medicalinformation@clonmel-health.ie	+353 52 6177777
Cooper Pharmaceuticals S.A.	Nafloxin 200mg/100ml, injectable solution for infusion	goulielmos@koper.gr sofianopoulou@koper.gr skoufi@koper.gr	+3069 49948615

		safety@excelya.com	
Delorbis Pharmaceuticals Ltd.	Viprolox 250mg film-coated tablets (ciprofloxacin hydrochloride 250mg), Viprolox 500mg film-coated tablets (ciprofloxacin 500mg), Floxaval 500mg film-coated (levofloxacin 500mg)	delorbis@delorbispharma.eu	+357 22 845 000
Farmarosib S.r.l.	Levofloxcina Arena 500mg film-coated tablets (levofloxacin 500mg)	antony.gauci@farmarosib.ro	+ 356 99075188
Fresenius Kabi Italia S.r.l.	Ciprofloxacin Kabi 200 mg/100 ml solution for infusion, Ciprofloxacin Kabi 400 mg/200 ml solution for infusion, Levofloxacin 5mg/ml solution for infusion	farmacovigilanza@fki-srl.legalmail.it	+39 0452053766 + 39 3489710480
Ibigen S.r.l.	Levofloxacin Ibigen solution for infusion 5mg/ml (50ml vial) (levofloxacin 5mg/ml) Levofloxacin Ibigen solution for infusion 5mg/ml (100ml vial) (levofloxacin)	safety@drugsalesltd.com	+356 21419070/1/2
JV Healthcare Ltd.	Ciplox 250 mg Film-coated Tablets (ciprofloxacin hydrochloride 250mg), Ciplox 500 mg Film-coated Tablet (ciprofloxacin hydrochloride 500mg)	info@jvpharma.eu	+356 21437551
Medochemie Ltd.	Medociprin (ciprofloxacin 500mg), Medociprin (ciprofloxacin 250mg), Amesol 500mg film–coated tablets (levofloxacin 500mg), Erelan 400mg film-coated tablet (moxifloxacin hydrochloride 400mg)	pharmacovigilance@medochemie.com alex.fenech@europharma.com.mt	+356 2385 9239
Neofarma Pharmaceuticals Ltd.	Ciprofloxacin Teva 250mg film-coated tablets (ciprofloxacin 250mg), Ciprofloxacin Teva 500mg film-coated tablets (ciprofloxacin 500mg), Ciproxin Tablets 500mg (ciprofloxacin hydrochloride 500mg), Ciprinol 250 mg film-coated tablets (ciprofloxacin 250mg), Ciprinol 500 mg film-coated tablets (ciprofloxacin 500mg), Tavanic Coated Tablets 500mg (Levofloxacin 500mg), Ciproxin 500mg (ciprofloxacin)	pc@neofarma.com.mt rp@neofarma.com.mt	+356 20109494
NM Pharma Ltd.	Ciprofloxacin Teva 250 mg film-coated tablets (ciprofloxacin hydrochloride monohydrate 250mg), Ciprofloxacin Teva 500 mg film-coated tablets (ciprofloxacin hydrochloride monohydrate 500mg), Ciprofloxacin Mylan 250mg film-coated tablets (ciprofloxacin 250mg), Ciprofloxacin Mylan 500mg film-coated tablets (ciprofloxacin 500mg)	ann@nmpharma.com.mt info@nmpharma.com.mt	+356 79310592
Noridem Enterprises Ltd.	Ciprofloxacin 2 mg/ml solution for infusion, Levofloxacin 5 mg/mL solution for infusion	pv@demo.gr	+30 2108161802
Norma Hellas S.A.	Revionorm solution for infusion 200mg/100ml (ciprofloxacin 2mg/ml)	safety@pharmassist-cro.com	+30 2106561435

Piam Farmaceutici	Trissil Tablet (levofloxacin hemihydrate 512.46mg)	pharmacovigilance@prohealth.com.mt	+356 23385313
Remedica Ltd.	Zindolin 250 mg Film-coated tablets (ciprofloxacin 250mg), Trizolin 400 mg Film-coated tablets (Norfloxacin 400mg),	a.vasiliou@remedica.com.cy drugsafety@remedica.com.cy	+357 25553251 +357 25553000
Rowex	Cifox Tablet, film coated 500mg (ciprofloxacin hydrochloride 500mg), Cifox Tablet, film coated 750mg (ciprofloxacin hydrochloride 750mg)	pharmacovigilance@prohealth.com.mt	+356 23385313
Sanofi S.r.l.	Tavanic 500 mg film-coated tablets (Levofloxacin 500mg)	pharmacovigilancemalta@sanofi.com pv@charlesdegiorgio.com	+39 0239394275 +356 9974 1387
TAD Pharma GmbH	Ciprinol 250 mg film-coated tablets (ciprofloxacin 250mg), Ciprinol 500 mg film-coated tablets (ciprofloxacin 500mg)	drug-safety@tad.de	+49 47216060

Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of A. Menarini - Industrie Farmaceutiche Riunite - S.r.l., Anfarm Hellas S.A., Azure Pharmaceuticals Ltd., Bayer Ltd., Clonmel Healthcare Ltd., Cooper Pharmaceuticals S.A., Delorbis Pharmaceuticals Ltd., Farmarosib S.r.l., Fresenius Kabi Italia S.r.l., Ibigen S.r.l., JV Healthcare Ltd., Medochemie Ltd., Neofarma Pharmaceuticals Ltd., NM Pharma Ltd., Noridem Enterprises Ltd., Norma Hellas S.A., Piam Farmaceutici, Remedica Ltd., Rowex, Sanofi S.r.l., TAD Pharma GmbH,.

The MMA receives the relevant contact details from both the Medical Council and the Pharmacy Council. Should you wish to amend your details including your postal address, you are asked to contact the Medical Council or Pharmacy Council directly, as may apply.