Javna agencija Republike Slovenije
za zdravila in medicinske pripomočke
Agency for Medicinal Products
and Medical Devices
of the Republic of Slovenia

Ptujska ulica 21
SI – 1000 Ljubljana
t + 386 (0)8 2000 500
f + 386 (0)8 2000 510
www.jazmp.si

Številka: 1382-3/2011
Datum : 10.2.2011

VSEM IMETNIKOM DOVOLJENJ ZA PROMET Z ZDRAVILI, KI VSEBUJEJO FLUOROKINOLONE

Zahteva za predložitev spremembe tipa IB – dopolnitev povzetka glavnih značilnosti zdravila in navodila za uporabo za zdravila, ki vsebujejo fluorokinolone

Spoštovani,

V januarju 2010 je delovna skupina za farmakovigilanco (PhVWP) pregledala in ocenila podatke o tveganju za podaljšanje intervala QT. Na osnovi ocene podatkov *in vitro* elektrofizioloških študij, *in vivo* študij in kliničnih podatkov je fluorokinolone razdelila v tri skupine glede na tveganje za podaljšanje intervala QT in predlagala, da se informacije v povzetku glavnih značilnosti zdravila in v navodilih za uporabo zadevnih zdravil ustrezno dopolnijo.

Imetnike dovoljenj za promet z zadevnimi zdravili, ki še niso predložili vloge za spremembo prosimo, da Javni agenciji RS za zdravila in medicinske pripomočke v skladu s Pravilnikom o dovoljenju za promet z zdravilom za uporabo v humani medicini (Uradni list RS, št. 109/2010) in obvestilom JAZMP glede nove Uredbe Komisije (ES) št.1234/2008 z dne 24.11.2008 o pregledu sprememb pogojev dovoljenj za promet z zdravili za uporabo v humani medicini in zdravili za uporabo v veterinarski medicini predložijo spremembo tipa IB najkasneje v 30 dneh od objave obvestila. Dodatne informacije in podporna dokumentacija v vlogi niso potrebne.

Rok za implementacijo spremembe je julij 2011.

V nadaljevanju vam podajamo odobreno originalno besedilo spremembe, objavljeno je tudi na spletni strani Vodij agencij za zdravila http://www.hma.eu/222.html.

S spoštovanjem,

dr. Martina Cvelbar, mag. farm., spec.
direktorica

Pripravila:
Katja Mohorčič, dipl.inž.lab.biomed.

- ***Gemifloxacin [1] and moxifloxacin***

SUMMARY OF PRODUCT CHARACTERISTICS

4.3 Contraindications

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to <X>, in the form of QT prolongation. For reasons of drug safety, <X> is therefore contraindicated in patients with:

- congenital or documented acquired QT prolongation,
- electrolyte disturbances, particularly in uncorrected hypokalaemia,
- clinically relevant bradycardia,
- clinically relevant heart failure with reduced left-ventricular ejection fraction,
- previous history of symptomatic arrhythmias,

<X> should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

4.4 Special warnings and precautions for use

For oral formulations

Prolongation of QTc interval and potentially QTc-prolongation related clinical conditions

<X> has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with <X> was <XY> msec ± <XZ> msec, <XX> compared to baseline. As women tend to have a longer baseline QT_c interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Medication that can reduce potassium levels should be used with caution in patients receiving <X>.

<X> should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest (see also section 4.3). The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

The benefit of <X> treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section.

If signs of cardiac arrhythmia occur during treatment with <X>, treatment should be stopped and an ECG should be performed.

For i.v. formulations of moxifloxacin

Prolongation of QTc interval and potentially QTc-prolongation related clinical conditions

Moxifloxacin has been shown to prolong the QT_c interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not be exceeded. For more details see below and refer to sections 4.3 and 4.5.

Treatment with moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.

Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. See also sections 4.3 and 4.5.

Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels. See also section 4.3.

Moxifloxacin should be used with caution in patients who are taking medications associated with clinically

[1] The MAH recently withdrew the MA application for gemifloxacin. Therefore, no SPC is currently approved for this product. Looking forward to the results of a QT-study according to the ICH E14, any future SPC for gemifloxacin should be similar to the moxifloxacin one regarding the risk of QT interval prolongation.

significant bradycardia. See also section 4.3.
Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as moxifloxacin and therefore special caution is required.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products

An additive effect on QT interval prolongation of <X> and other medicinal products that may prolong the QT_c interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore co-administration of <X> with any of the following medicinal products is contraindicated (see also section 4.3):

- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).
-

4.8 Undesirable effects

For oral formulations

Cardiac and vascular disorders:

<frequency to be specified according to the results of clinical trials with the product>: QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)

<frequency to be specified according to the results of clinical trials with the product>: QT prolongation (see section 4.4)

<frequency to be specified according to the results of clinical trials with the product>: ventricular tachyarrhythmias, syncope (i.e., acute and short lasting loss of consciousness)

<frequency to be specified according to the results of clinical trials with the product>: unspecified arrhythmias, torsade de pointes (see section 4.4), cardiac arrest (see section 4.4)

For i.v. formulations of moxifloxacin

The following undesirable effects have a higher frequency category in the subgroup of IV treated patients with or without subsequent oral therapy:

Uncommon: ventricular tachyarrhythmias.

4.9 Overdose

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

PACKAGE LEAFLET

2. BEFORE YOU TAKE <X>

Do not take <X>

- If you were born with or have had any condition with abnormal heart rhythm (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called 'bradycardia'), have a weak heart (heart failure), have a history of abnormal heart rhythms, or you are taking other medicines that result in abnormal ECG changes (see section *Taking other medicines*).
  This is because <X> can cause changes on the ECG, that is a prolongation of the QT-interval i.e. delayed conduction of electrical signals.

Take special care with <X>

Before taking <X>

- <X> can **change your heart's ECG**, especially if you are female, or if you are elderly. If you are currently taking any medicine that decrease your blood potassium levels, consult your doctor before taking <X>.

When taking <X>

- If you experience palpitations or irregular heart beat during the period of treatment, you should inform your

doctor immediately. He/she may wish to perform an ECG to measure your heart rhythm.

- The **risk of heart problems** may increase with increase of the dose. Therefore, the recommended dosage should be followed. *(for oral formulations)*
- The **risk of heart problems** may increase with increase of the dose and the speed of the perfusion into your vein. *(for intravenous formulations)*

Taking other medicines

For <X>, be aware of the following:

- If you are taking <X> and other medicines that affect your heart there is an increased risk for altering your heart rhythm. Therefore, do not take <X> together with the following medicines: medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride), tricyclic antidepressants, some antimicrobials (e.g. sparfloxacin, intravenous erythromycin, pentamidine, antimalarials particularly halofantrine), some antihistamines (e.g. terfenadine, astemizole, mizolastine), and other medicines (e.g. cisapride, intravenous vincamine, bepridil and diphemanil).
- You must tell your doctor if you are taking other medicines that can lower your blood potassium levels or cause a slow heart rate because these can also increase the risk of serious heart rhythm disturbances while taking <X>.

4. POSSIBLE SIDE EFFECTS

Cardiac System (see section *2. Before you take <X>.*)

<frequency to be specified according to the results of clinical trials with the product>:

Change of the heart rhythm (ECG) in patients with low blood potassium level

Change of the heart rhythm (ECG), palpitations, irregular and fast heart beat, severe heart rhythm abnormalities, angina pectoris

Abnormal fast heart rhythm, fainting

Abnormal heart rhythms, life-threatening irregular heart beat, stopping of heart beat

For i.v. formulations of moxifloxacin

The following symptoms have been observed more frequently in patients treated intravenously:

<frequency to be specified according to the results of clinical trials with the product>:

Abnormal fast heart rhythm

- ***Levofloxacin, norfloxacin, ofloxacin***

SUMMARY OF PRODUCT CHARACTERISTICS

4.4 Special warnings and precautions for use

Cardiac disorders

Caution should be taken when using fluoroquinolones, including <X>, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

(See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Drugs known to prolong QT interval

<X>, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

4.8 Undesirable effects

Cardiac disorders

Not known : ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9).

4.9 Overdose

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

PACKAGE LEAFLET

2. BEFORE YOU TAKE <X>

Take special care with <X>

Before taking <X>

Heart problems

Caution should be taken when using this kind of medicine, if you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called 'bradycardia'), have a weak heart (heart failure), have a history of heart attack (myocardial infarction), you are female or elderly or you are taking other medicines that result in abnormal ECG changes (see section *Taking other medicines*).

Taking other medicines

You must tell your doctor if you are taking other medicines that can alter your heart rhythm: medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), tricyclic antidepressants, some antimicrobials (that belong to the group of macrolides), some antipsychotics.

4. POSSIBLE SIDE EFFECTS

Heart problems

Not known: Abnormal fast heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm (called 'prolongation of QT interval', seen on ECG, electrical activity of the heart)

- ***Enoxacin, pefloxacin, prulifloxacin and rufloxacin***

SUMMARY OF PRODUCT CHARACTERISTICS

4.4 Special warnings and precautions for use

Cardiac disorders

Some other substances from the fluoroquinolone class have been associated with cases of QT interval prolongation.

4.8 Undesirable effects

To be completed with the appropriate frequency if cases have been reported.

PACKAGE LEAFLET

2. BEFORE YOU TAKE <X>

Take special care with <X>

Before taking <X>

Heart problems

Since alterations of the heart rhythm (seen on ECG, electrical reconding of the heart) have been reported with other antibiotics belonging to the group of the fluoroquinolones, tell your doctor if you have a history of abnormal heart rhythm.

4. POSSIBLE SIDE EFFECTS

To be completed with the appropriate frequency if cases have been reported.