Public Assessment Report

Decentralised Procedure

MOXIFLOXACIN 400 MG FILM-COATED TABLETS
(moxifloxacin hydrochloride)

Procedure No: UK/H/6718/001/DC

UK Licence No: PL 11311/0583

Tilomed Laboratories Limited
LAY SUMMARY
Moxifloxacin 400 mg film-coated tablets
(moxifloxacin hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Moxifloxacin 400 mg film-coated tablets (PL 11311/0583; UK/H/6718/001/DC). It explains how the application for Moxifloxacin 400 mg film-coated tablets was assessed and its authorisation recommended as well as the conditions of use. It is not intended to provide practical advice on how to use Moxifloxacin 400 mg film-coated tablets.

For practical information about using Moxifloxacin 400 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

For ease of reading, this product will be referred to as Moxifloxacin tablets for the remainder of this summary.

What are Moxifloxacin tablets and what are they used for?
Moxifloxacin tablets are a ‘generic medicine’. This means that Moxifloxacin tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Avelox 400 mg Film-coated Tablets.

Moxifloxacin tablets are used in patients aged 18 years and above for treating the following bacterial infections when caused by bacteria against which moxifloxacin is active. Moxifloxacin should only be used to treat these infections when usual antibiotics cannot be used or have not worked:

- Infection of the sinuses, sudden worsening of long-term inflammation of the airways or infection of the lungs (pneumonia) acquired outside the hospital (except severe cases).
- Mild to moderate infections of the female upper genital tract (pelvic inflammatory disease), including infections of the fallopian tubes and infections of the uterus mucous membrane.

Moxifloxacin tablets are not sufficient on their own for treating this kind of infection. Therefore, another antibiotic in addition to Moxifloxacin tablets should be prescribed by your doctor for the treatment of infections of the female upper genital tract.

If the following bacterial infections have shown improvement during initial treatment with Moxifloxacin solution for infusion, Moxifloxacin tablets may also be prescribed by your doctor to complete the course of therapy:

- Infection of the lungs (pneumonia) acquired outside the hospital,
- Infections of the skin and soft tissue.

Moxifloxacin tablets should not be used to initiate therapy for any type of infections of the skin and soft tissue or in severe infections of the lungs.

How do Moxifloxacin tablets work?
This medicine contains the active ingredient moxifloxacin hydrochloride, which belongs to a group of antibiotics called fluoroquinolones. Moxifloxacin works by killing bacteria that cause infections.

How are Moxifloxacin tablets used?
These medicines can only be obtained with a prescription.

The recommended dose for adults is one 400 mg film-coated tablet once daily.

Moxifloxacin tablets are for oral use. The tablet should be swallowed whole (to mask the bitter taste) and with plenty of liquid. Patients can take Moxifloxacin tablets with or without food and should try to take the tablet at approximately the same time each day.
The same dose can be taken by elderly patients, patients with a low bodyweight or in patients with kidney problems.

The length of time a patient will take Moxifloxacin tablets depends on their infection. Unless advised by a doctor, the treatment will be as follows:
- for sudden worsening (acute exacerbation) of chronic bronchitis: 5 - 10 days
- for infection of the lungs (pneumonia) except for pneumonia which starts during a stay in hospital: 10 days
- for acute infection of the sinuses (acute bacterial sinusitis): 7 days
- for mild to moderate infections of the female upper genital tract (pelvic inflammatory disease), including infection of the fallopian tubes and infection of the uterus mucous membrane: 14 days

When Moxifloxacin tablets are used to complete a course of therapy started with Moxifloxacin solution for infusion, the recommended durations of use are:
- Infection of the lungs (pneumonia) acquired outside the hospital: 7 - 14 days. Most patients with pneumonia are switched to oral treatment with Moxifloxacin tablets within 4 days.
- Infections of the skin and soft tissue: 7 - 21 days. Most patients with infections of the skin and soft tissue are switched to oral treatment with Moxifloxacin film-coated tablets within 6 days.

It is important that patients complete the course of treatment even if they begin to feel better after a few days.

If patients stop taking Moxifloxacin tablets too soon their infection may not be completely cured and the infection may return, or their condition may get worse. The bacteria causing the infection may become resistant to moxifloxacin.

The recommended dose and duration of treatment should not be exceeded.

**What benefits of Moxifloxacin tablets have been shown in studies?**
Because Moxifloxacin tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Avelox 400 mg Film-coated Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body

**What are the possible side effects of Moxifloxacin tablets?**
Because Moxifloxacin tablets are a generic medicine, their possible side effects are taken as being the same as those of the reference medicine, Avelox 400 mg Film-coated Tablets.

For the full list of all side effects reported with Moxifloxacin tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why were Moxifloxacin tablets approved?**
It was concluded that, in accordance with EU requirements, Moxifloxacin tablets have been shown to have comparable quality and to be bioequivalent to Avelox 400 mg Film-coated Tablets. Therefore, the MHRA decided that, as for Avelox 400 mg Film-coated Tablets, the benefits outweigh the identified risks and recommended that Moxifloxacin tablets can be approved for use.

**What measures are being taken to ensure the safe and effective use of Moxifloxacin tablets?**
A risk management plan (RMP) has been developed to ensure that Moxifloxacin tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Moxifloxacin tablets including the appropriate precautions to be followed by healthcare professionals and patients.
Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Moxifloxacin tablets**
Germany, Spain and the UK agreed to grant Marketing Authorisations for Moxifloxacin 400 mg film-coated tablets on 01 August 2018.

Following a National phase, a Marketing Authorisation was granted in the UK on 31 August 2018.

The full PAR for Moxifloxacin tablets follows this summary. For more information about treatment with Moxifloxacin tablets read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2018.
SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Moxifloxacin 400 mg film-coated tablets (PL 11311/0583; UK/H/6718/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and Spain and Germany as Concerned Member States (CMS).

This product is a prescription only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Avelox 400 mg Film-coated Tablets (PL 00010/0291), which was initially granted a Marketing Authorisation to Bayer plc, in the UK, on 13 March 2003.

Moxifloxacin 400 mg film-coated tablets are indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin. Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections or when these have failed:

- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia, except severe cases
- Acute bacterial sinusitis (adequately diagnosed)
- Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.

Moxifloxacin 400 mg film-coated tablets are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of Neisseria gonorrhoeae unless moxifloxacin-resistant Neisseria gonorrhoeae can be excluded.

Moxifloxacin 400 mg film-coated tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:

- Community-acquired pneumonia
- Complicated skin and skin structure infections

Moxifloxacin tablets should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This product contains the active substance moxifloxacin hydrochloride, which is a fluoroquinolone antibiotic. Moxifloxacin has in vitro activity against a wide range of Gram-positive and Gram-negative pathogens. The bactericidal action of moxifloxacin results from the inhibition of both type II topoisomerases (DNA gyrase and topoisomerase IV) required for bacterial DNA replication, transcription and repair. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the norA or pmrA genes seen in certain Gram-positive bacteria. Pharmacodynamic investigations have demonstrated that moxifloxacin exhibits a concentration dependent killing rate. Minimum bactericidal concentrations (MBC) were found to be in the range of the minimum inhibitory concentrations (MIC).

With the exception of the bioequivalence study, no new clinical or non-clinical studies were conducted,
which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was performed which compared the pharmacokinetics of the test product, Moxifloxacin 400 mg film-coated tablets, to those of the reference product Avalox 400 mg Film-coated Tablets (Bayer Vital GmbH, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 01 August 2018. After a subsequent national phase, a licence was granted in the UK on 31 August 2018.

II QUALITY ASPECTS
II.1 Introduction
Moxifloxacin 400 mg film-coated tablets are dull red coloured, caplet shaped tablets, with a dimension of 17 x 7 mm, debossed with "400" on one side and “M” on other side. Each film-coated tablet contains 400 mg moxifloxacin hydrochloride.

Other ingredients consist of the pharmaceutical excipients, as follows:
Tablet core: Povidone (K-29/32), croscarmellose sodium, lactose monohydrate, anhydrous lactose, colloidal anhydrous silica, magnesium stearate
Film-coat: Hypromellose 6cP, titanium dioxide (E171), macrogol 400, red iron oxide (E172)

The finished product is packaged in polyvinyl chloride/polyvinylidene chloride/aluminium blisters in pack sizes of 5, 7, 10 and 14 tablets. Not all pack-sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance
INN: Moxifloxacin
Chemical name: 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

Structure:

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Molecular formula: C21H24FN3O4.HCl.H2O
Molecular weight: 455.9
Appearance: Light yellow or yellow powder or crystals
Solubility: Sparingly soluble in water, slightly soluble in ethanol (96%), practically insoluble in acetone
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All aspects of the manufacture and control of the active substance moxifloxacin hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of
II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a stable product that could be considered a generic medicinal product of the currently licensed product, Avelox 400 mg Film-coated Tablets (Bayer plc).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the applicant’s product versus the reference product.

With the exception of the tablet coating, which complies with an in-house specification, all excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. The magnesium stearate is of vegetable origin. This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three pilot scale batches of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf life of 3 years, with the special storage conditions of “Store in the original package in order to protect from moisture”.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Moxifloxacin 400 mg film-coated tablets.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of moxifloxacin hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As this product is intended for generic substitution of a product that is already marketed, no increase in environmental exposure to moxifloxacin hydrochloride is anticipated. Thus, the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Moxifloxacin 400 mg film-coated tablets.

IV. CLINICAL ASPECTS
IV.1 Introduction
With the exception of the bioequivalence study detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

Study 1:
A single centre, open label, randomised, single dose, two-way crossover bioequivalence study comparing the pharmacokinetics of the test product, Moxifloxacin 400 mg film-coated tablets, to those of the reference product, Avalox 400 mg Film-coated Tablets (Bayer Vital GmbH, Germany), in healthy, adult, human subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each treatment was separated by a washout period of 7 days.

A summary of the main pharmacokinetic results is presented in the table below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference (R)</th>
<th>Test (T)</th>
<th>100*(T/R) Ratio</th>
<th>CI (%)</th>
<th>Intra CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>4291.05</td>
<td>4544.09</td>
<td>105.90</td>
<td>98.48 - 113.88</td>
<td>16.04</td>
</tr>
<tr>
<td>AUC_{0-4h} (ng x hr/mL)</td>
<td>50110.70</td>
<td>49671.07</td>
<td>99.12</td>
<td>97.67 - 100.60</td>
<td>3.24</td>
</tr>
<tr>
<td>AUC_{0-4} (ng x hr/mL)</td>
<td>52089.26</td>
<td>51587.95</td>
<td>99.04</td>
<td>97.80 - 100.29</td>
<td>2.76</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for moxifloxacin for the ratio of test/reference are within 80.00-125.00% for C_{max} and AUC. Moxifloxacin 400 mg film-coated tablets are, therefore, considered bioequivalent to Avelox 400 mg Film-coated Tablets (Bayer plc).
IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Moxifloxacin 400 mg film-coated tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
</table>
| Hypersensitivity including anaphylaxis | • Contraindication in SPC Section 4.3 and PIL Section 2 for patients with hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.  
• Warning in SPC Section 4.4 and PIL Section 2 mention that hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration.  
• Listed in SPC Section 4.8 and PIL Section 4: Allergic reaction, anaphylaxis including very rarely life-threatening shock, allergic oedema / angioedema (including laryngeal oedema, potentially life-threatening).  
• Prescription-only medicine | None proposed |
| Prolongation of QTc interval | • Contraindication in SPC Section 4.3 and PIL Section 2 for patients with congenital or documented acquired QT prolongation and electrolyte disturbances, particularly in uncorrected hypokalaemia  
• Warning in SPC Section 4.4 and PIL Section 2 mention that moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients.  
• Interaction in SPC Section 4.5 and PIL Section 2 states that an additive effect on QT interval prolongation of | None proposed |
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>moxifloxacin and other medicinal products that may prolong the QTc interval cannot be excluded.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: QT prolongation in patients with hypokalaemia, QT prolongation, Torsade de Pointes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Information in SPC Section 5.3 states that at high concentrations, moxifloxacin may cause prolongations of the QT interval.</td>
<td></td>
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<tr>
<td></td>
<td>• Prescription-only medicine</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>• Warning in SPC Section 4.4 and PIL Section 2 mention that quinolones are known to trigger seizures.</td>
<td>None proposed</td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: Seizures incl. grand mal convulsions.</td>
<td></td>
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<tr>
<td></td>
<td>• Prescription-only medicine</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>• Warning in SPC Section 4.4 and PIL Section 2 mention that cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin.</td>
<td>None proposed</td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine</td>
<td></td>
</tr>
<tr>
<td>Tendinopathy</td>
<td>• Contraindication in SPC Section 4.3 and PIL Section 2 for patients with a history of tendon disease/disorder related to quinolone treatment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Warning in SPC Section 4.4 and PIL Section 2 mention that tendon inflammation and rupture (especially Achilles tendon), sometimes bilateral, may occur with quinolone therapy including moxifloxacin, even within 48 hours of starting treatment and have been reported up to several months</td>
<td></td>
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<tr>
<td>Safety Concern</td>
<td>Routine Risk Minimisation Measures</td>
<td>Additional Risk Minimisation Measures</td>
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<tr>
<td></td>
<td>after discontinuation of therapy</td>
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<tr>
<td></td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: Tendonitis, Tendon rupture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine</td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>• Warning in SPC Section 4.4 and PIL Section 2 mention that cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with moxifloxacin.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: Increase in transaminases, hepatic impairment (incl. LDH increase), increased bilirubin, increased gammaglutamyl transferase, and increase in blood alkaline phosphatase, jaundice, hepatitis (predominantly cholestatic), fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)</td>
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<tr>
<td></td>
<td>• Information in SPC Section 5.3 states that hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs</td>
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<tr>
<td></td>
<td>• Prescription-only medicine</td>
<td></td>
</tr>
<tr>
<td>Antibiotic associated diarrhoea (including colitis)</td>
<td>• Warning in SPC Section 4.4 and PIL Section 2 mention that Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis.</td>
<td></td>
</tr>
<tr>
<td>in hospital setting</td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: Antibiotic associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine</td>
<td></td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine Risk Minimisation Measures</td>
<td>Additional Risk Minimisation Measures</td>
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</tbody>
</table>
| Renal failure                  | • Warning in SPC Section 4.4 and PIL Section 2 mention that elderly patients with renal disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.  
  • Listed in SPC Section 4.8 and PIL Section 4: Renal impairment (incl. increase in BUN and creatinine), renal failure.  
  • SPC Section 5.2 states that the pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment.  
  • Prescription-only medicine |                                                                                                                                            |                                      |
| Serious vision disorders       | • Warning in SPC Section 4.4 and PIL Section 2 mention that if vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.  
  • Information in SPC Section 4.7 states that fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. acute, transient loss of vision).  
  • Listed in SPC Section 4.8 and PIL Section 4: Visual disturbances incl. diplopia and blurred vision and transient loss of vision (especially in the course of CNS reactions)  
  • Prescription-only medicine |                                                                                                                                            |                                      |
| Serious bullous skin reactions | • Warning in SPC Section 4.4 and PIL Section 2 mention that cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin.  
  • Listed in SPC Section 4.8 and PIL Section 4: Bullous skin reactions like |                                                                                                                                            |                                      |
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening)</td>
<td>* Prescription-only medicine</td>
<td></td>
</tr>
</tbody>
</table>
| Depression, suicidality and psychosis | * Warning in SPC Section 4.4 and PIL Section 2 mention that psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin.  
* Listed in SPC Section 4.8 and PIL Section 4: Depression and psychotic reactions (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/thoughts, or suicide attempts) | * Prescription-only medicine           |
| Serious haematological disorders      | * Interaction in SPC Section 4.5 and PIL Section 2 mention that a large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibacterial agents, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins.  
* Listed in SPC Section 4.8 and PIL Section 4: Anaemia, leucopenia, neutropenia, thrombocytopenia, thrombocytthemia, blood eosinophilia, prothrombin time prolonged/INR increased, prothrombin level increased/INR decreased, agranulocytosis and haemolytic anaemia  
* SPC Section 5.3 states that effects on the haematopoetic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys.  
* Prescription-only medicine |                                       |
<p>| Exacerbation of myasthenia gravis     | * Warning in SPC Section 4.4 and PIL Section 2 mention that moxifloxacin should be used with caution in patients                                                                                                                        |                                       |</p>
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with myasthenia gravis because the symptoms can be exacerbated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8 and PIL Section 4: exacerbation of symptoms of myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine</td>
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</tbody>
</table>

### Important Potential Risks

|                |                                      |                                      |
| Bradycardia    | • Contraindication in SPC Section 4.3 and PIL Section 2 for patients with clinically relevant bradycardia. | None proposed                        |
|                | • Interaction in SPC Section 4.5 and PIL Section 2 mentions that Moxifloxacin should be used with caution in patients who are taking medication that is associated with clinically significant bradycardia. |                                      |
|                | • Prescription-only medicine         |                                      |
| Rhabdomyolysis, myositis and myopathy | • Listed in SPC Section 4.8 and PIL Section 4: Muscle cramp, muscle twitching, muscle weakness and rhabdomyolysis  | None proposed                        |
|                | • Prescription-only medicine         |                                      |
| Muscle rupture | • None proposed in SmPC and PIL. MAH will collect, process and report (to applicable regulatory authority) information on use of moxifloxacin and muscle rupture. | None proposed                        |
|                | • Prescription-only medicine         |                                      |
| Ligament rupture | • None proposed in SmPC and PIL. MAH will collect, process and report (to applicable regulatory authority) information on use of moxifloxacin and ligament rupture. | None proposed                        |
|                | • Prescription-only medicine         |                                      |
| Selection of drug resistant isolates  | • Special warning and precautions in SPC Section 4.4 and PIL Section 2 regarding use of moxifloxacin in patients with complicated pelvic inflammatory disease and patients with | None proposed                        |
### Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Moxifloxacin 400 mg film-coated tablets.

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
</table>
| MRSA infections. | • Listed in SPC Section 4.8 and PIL Section 4: Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis  
• SPC Section 5.1 states that resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may also affect susceptibility to moxifloxacin.  
• Prescription-only medicine | |
| Retinal detachment | • Information in SPC Section 5.3 mention that high oral doses of moxifloxacin (≥ 60 mg/kg) leading to plasma concentrations ≥ 20 mg/l caused changes in the electroretinogram and in isolated cases an atrophy of the retina  
• Prescription-only medicine | |
| Use of moxifloxacin in children and growing adolescents | • Posology in SPC Sections 4.2, contraindication in SPC Section 4.3, Warning in SPC Section 4.4 and PIL Sections 2 mentions that efficacy and safety of moxifloxacin in children and adolescents have not been established  
• Prescription-only medicine | None proposed |
| Arthropathy (in paediatric patients) | • SPC Section 5.3 states that Quinolones are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals.  
• Prescription-only medicine | None proposed |
V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with moxifloxacin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling is shown below:
Moxifloxacin 400 mg film-coated tablets

For Adults

Each film coated tablet contains 400 mg of moxifloxacin (as hydrochloride).
It also contains lactose (see leaflet for further information).

Opin use:
Read the package leaflet before use.
Keep out of the sight and reach of children.
This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

Marketing Authorisation Holder:
Tillomed Laboratories Ltd
220 Butterfield, Great Marlings,
Luton, LU2 8DL, UK
MA Number: PL 11311/0583

Code No: TS/DRUGS/5/2014

PAR Moxifloxacin 400 mg film coated tablets

UK/H/6718/001/DC
Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
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<td></td>
<td>Y/N (version)</td>
</tr>
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