# ANNEX I

# LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S) OF THE MEDICINAL PRODUCT(S), ROUTE(S) OF ADMINISTRATION, APPLICANT(S) MARKETING AUTHORISATION HOLDER(S) IN THE MEMBER STATES

| **Member State** | **Marketing Authorisation Holder** | **Invented name Name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| AT - Austria | Bayer HealthCare AG<br>51368 Leverkusen<br>Germany | Octegra 400 mg - Filmtabletten | 400 mg | Film-coated tablet | Oral use |
| BE - Belgium | THERABEL PHARMA S.A.<br>Rue Egide Van Ophem 108<br>1180 BRUXELLES | PROFLOX 400 MG | 400 mg | Film-coated tablet | Oral use |
| DE - Germany | Bayer HealthCare AG<br>51368 Leverkusen<br>Germany | Octegra 400 mg Filmtabletten | 400 mg | Film-coated tablet | Oral use |
| EL - Greece | ELPEN A.E. Pharmaceutical Industry<br>95 Marathonos Av.<br>190 09 Pikermi- Attica- Athens<br>Greece | Octegra | 400 mg | Film-coated tablet | Oral use |
| ES - Spain | Procter and Gamble Pharmaceuticals Iberia, SL<br>WTC Almeda park, edificio 1, 2º planta<br>Cornellá de Llobregat – Barcelona<br>Spain | OCTEGRA 400 mg comprimidos recubiertos con película | 400 mg | Film-coated tablet | Oral use |
| FR - France | Bayer HealthCare AG<br>51368 Leverkusen<br>Germany | OCTEGRA 400 mg, comprimé pelliculé | 400 mg | Film-coated tablet | Oral use |
| IT - Italy | Innova Pharma S.p.A.<br>Via M. Civitali, 1<br>20148 Milano<br>Italy | OCTEGRA | 400 mg | Film-coated tablet | Oral use |
| LU- Luxembourg | Therabel Pharma<br>110 Rue Egide Van Ochem<br>B 1180 Bruxelles<br>Belgium | Proflox | 400 mg | Film-coated tablet | Oral use |
| NL - Netherlands | Bayer Healthcare AG<br>51368 Leverkusen<br>Germany | Octegra 400 mg tabletten | 400 mg | Film-coated tablet | Oral use |

| | | | | |
|---|---|---|---|---|
| PT - Portugal | Bialfar - Produtos Farmacêuticos, S.A.<br>À Av. da Siderurgia Nacional<br>P.O. Box 56<br>4745-457 S. Mamede do Coronado<br>Portugal | Proflox | 400 mg | Film-coated tablet | Oral use |

**ANNEX II**

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE EMEA**

## SCIENTIFIC CONCLUSIONS

### Introduction

Octegra film-coated tablets contain 400 mg moxifloxacin as hydrochloride. It is approved for the treatment of the following bacterial infections if they are caused by bacteria susceptible to moxifloxacin:
- Acute exacerbation of chronic bronchitis
- Community acquired pneumonia, except severe cases
- Acute bacterial sinusitis (adequately diagnosed).

The tablets have to be taken orally once daily for up to 10 days, depending on the indication. In clinical trials the tablets have been studied for up to 14 days treatment. Octegra was initially approved in June 1999.

This procedure is a referral following a Mutual Recognition Procedure concerning the above variation application which was submitted for Octegra film-coated tablets to Germany as Reference Member State (RMS) and the Concerned Member States (CMS) AT, BE, EL, ES, FR, IT, LU, NL and PT on 5 December 2006. This Mutual Recognition variation procedure was started on 7 December 2006.

The MRP variation application DE/H/156/01/II/34 concerned an extension of the indication to include the treatment of mild to moderate pelvic inflammatory disease (PID), i.e. infections of upper genital tract, including salpingitis and endometritis.

Objections and concerns over the efficacy and safety of Octegra in the proposed indication were raised during the Mutual Recognition variation procedure. In view of these concerns, during the Mutual Recognition Procedure, Belgium considered that a positive benefit / risk balance had not been demonstrated and more robust evidence should be submitted in order to grant the indication applied for.

As these concerns were not resolved during the course of the variation procedure, a notification of an official referral for Arbitration, under Article 6(12) of Commission Regulation EC No 1084/2003, to the CHMP was made by Belgium on 19 October 2007.

The main unresolved areas of concern identified by Belgium were in terms of efficacy the emergence of moxifloxacin-resistant strains of *N. gonorrhoeae* and the feasibility of the treatment in the proposed indication in clinical practice. In terms of safety the longer treatment duration, the risk of effects on cartilage in young patients and the risk of QT-prolongation were of concern.

The Referral procedure was initiated on 15 November 2007 with the adoption of a CHMP List of Questions to be addressed by the MAHs.

### Efficacy

It became evident during the course of the variation preceding this referral that an empirical therapy of PID with moxifloxacin should be avoided due to the high portion of *N. gonorrhoeae* being resistant to moxifloxacin and other quinolones. However it was questioned that this might not be compatible with clinical practice.

The review of available guidelines and clinical efficacy data showed that moxifloxacin can be used for treatment of PID in the sense of a monotherapy only after results of microbiological testing are available. In clinical practice these cases are usually restricted to cases when a combination with an approved agent active against fluoroquinolone resistant N. gonorrhoeae is not possible or in cases of therapeutic failure with a different therapy.

The CHMP considered that due to the emergence of fluoroquinolone-resistant *N. gonorrhoeae* strains moxifloxacin should not be used in empirical monotherapy of mild to moderate PID, unless a resistance against moxifloxacin can be ruled out. In clinical practice, this would mean that moxifloxacin should be used in combination with an approved agent active against fluoroquinolone resistant N. gonorrhoeae (e.g. a cephalosporin) for empirical treatment of PID unless moxifloxacin-resistant N. gonorrhoeae can be excluded.

To cover all etiologic agents of PID a combination with another antibiotic class such as the cephalosporins (e.g. ceftriaxone 250 mg intramuscular (IM) in a single dose) should be given empirically, which would be similar to other recommended treatment regimens given in combination.

Although it is well known that monotherapy increases compliance, this example of combination therapy would not decrease compliance since the proposed cephalosporin would only have to be given once during the physician's visit and only moxifloxacin would have to be continued orally. Although it is acknowledged that approximately 95% of the women with a PID might be 'overtreated' by this combination therapy this fact outweighs the potential risk of not treating approximately 5% of a mainly very young population which could develop serious long-term sequelae.

**Safety**

In this referral procedure, the CHMP focused on the risk of more frequent QT-prolongation in women in the light of the prolonged treatment regimen in PID (14 days vs. 5-10 days), on the risk of coadministration with other QT-affecting substances and on the possible adverse effects on cartilage in the treatment population.

QT-prolongation is a known undesirable effect of moxifloxacin. Available data demonstrated no evidence for increased cardiac morbidity related to oral moxifloxacin therapy when compared to comparator antibiotic therapy, especially in a younger female population, although in other trials QT interval prolongation and torsades de pointes were more common in women than in men. Women with PID are generally young women with few underlying diseases and concomitant medications. The analysis of the incidence of cardiac adverse events did not reveal any special subgroups of PID patients for whom moxifloxacin presents a greater risk than comparator treatments.

The CHMP considered that in general women treated for PID for up to 14 days are not at an increased risk of cardiac adverse events compared to the shorter treatment duration in the other indications.

Concerning overall cardiac adverse events, no differences between short (up to 5 days) and longer duration (up to 15 days) of moxifloxacin therapy were observed. In addition, the risk of QT-prolongation is already sufficiently addressed in the Product Information and will be adequately followed up by the MAH in the post-marketing setting.

The CHMP considered that QT-prolongation in PID should however be carefully addressed by the MAH in future PSURs. The MAH committed to monitor this adverse event in the next PSURS and committed to provide an updated Risk Management Plan taking into account the new indication mild to moderate PID.

Due to the potential risk of adverse effects on the cartilage in patients under the age of 18 years, and the fact that PID mostly affects young women, the existing wording of the contraindication in children and adolescents was further specified namely that it is contraindicated in patients below 18 years of age.

Overall, the CHMP agreed that the benefit/risk balance of moxifloxacin in the PID indication over 14 days is positive. Information and recommendations regarding taking measures before prescribing moxifloxacin are adequately addressed in the 'contraindications' and 'warnings-precaution of use' sections of the SPC and PL.

**GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET**

- The Committee considered the Referral made under Article 6(12) of Commission Regulation (EC) No 1084/2003, for Octegra and associated names (See Annex 1).

- The Committee considered that robust data is available showing the efficacy of Octegra in the indication "T*reatment of mild to moderate pelvic inflammatory disease (PID), i.e. infections of upper genital tract, including salpingitis and endometritis*" , however due to emerging resistance of *N. gonorrhoeae*, moxifloxacin should not be used in empirical monotherapy, unless moxifloxacin-resistant *N. gonorrhoeae* can be excluded.

- The Committee considered that no additional safety concerns were expected with the claimed indication in comparison to the previously approved indications.

- The Committee, in view of the presented data on efficacy and safety, considered that the Benefit / Risk balance for Octegra and associated names in the " *The treatment of mild to moderate pelvic inflammatory disease (PID), i.e. infections of upper genital tract, including salpingitis and endometritis"* with the restrictions concerning empirical monotherapy was favourable;

- The CHMP, as a consequence, recommended the amendment of the Summary of Product Characteristics sections 4.1, 4.2, 4.3, 4.4, 5.1 and 5.2 and Package Leaflet relevant sections as set out in Annex III for Octegra and associated names (see Annex I).

**ANNEX III**

**AMENDMENTS TO SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET (RELEVANT SECTIONS ONLY)**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[Invented name] 400 mg film-coated tablets are indicated for the treatment of the following bacterial infections:

- Acute exacerbation of chronic bronchitis
- 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. [Invented name] 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 (see sections 4.4 and 5.1).

[Invented name] 400 mg film-coated tablets are indicated for the treatment of the above infections if they are caused by bacteria susceptible to moxifloxacin.

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

### 4.2 Posology and method of administration

Dosage (adults)
One 400 mg film-coated tablet once daily.

Renal/hepatic impairment
No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis (see section 5.2 for more details).
There is insufficient data in patients with impaired liver function (see section 4.3).

Other special populations
No adjustment of dosage is required in the elderly and in patients with low bodyweight.

Children and adolescents
Moxifloxacin is contraindicated in children and adolescents (< 18 years). Efficacy and safety of moxifloxacin in children and adolescents have not been established (see section 4.3).

Method of administration
The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

Duration of administration
[Invented name] 400 mg film-coated tablets should be used for the following treatment durations:

- Acute exacerbation of chronic bronchitis 5 - 10 days
- Community acquired pneumonia 10 days
- Acute sinusitis 7 days
- Mild to moderate pelvic inflammatory disease 14 days

[Invented name] 400 mg film-coated tablets have been studied in clinical trials for up to 14 days treatment.

The recommended dose (400 mg once daily) and duration of therapy for the indication being treated should not be exceeded.

## 4.3 Contraindications

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.
- Pregnancy and lactation (see section 4.6).
- Patients below 18 years of age.
- Patients with a history of tendon disease/disorder related to quinolone treatment.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin 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

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

Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN.

## 4.4 Special warnings and precautions for use

- Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In these cases moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.
- Moxifloxacin 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 moxifloxacin was 6 msec ± 26 msec, 1.4% compared to baseline.
  Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin.
  Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as acute myocardial ischaemia 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 moxifloxacin 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 moxifloxacin, treatment should be stopped and an ECG should be performed.

- Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.
  Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.
- Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders which may predispose to seizures or lower the seizure threshold.
- Antibiotic associated colitis (incl. pseudomembranous colitis) has been reported in association with the use of broad spectrum antibiotics including moxifloxacin; therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. In this situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.
- Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin and rest the affected limb(s).
- 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.
- If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
- Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Nevertheless patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin.
- Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with [Invented name] 400 mg film-coated tablets is not recommended.
- Pelvic inflammatory disease may be caused by fluoroquinolone resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.
- Due to adverse effects on the cartilage in juvenile animals (see section 5.3) the use of moxifloxacin in children and adolescents < 18 years is contraindicated (see section 4.3).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01 MA 14

Mechanism of action
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 *nor*A or *pmr*A 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).

Interference with culture test
Moxifloxacin therapy may give false negative culture results for *Mycobacterium* spp. by suppression of mycobacterial growth.

Effect on the intestinal flora in humans
The following changes in the intestinal flora were seen in volunteers following oral administration of moxifloxacin: *Escherichia coli*, *Bacillus* spp., *Enterococcus* spp., and *Klebsiella* spp. were reduced, as were the anaerobes *Bacteroides vulgatus*, *Bifidobacterium* spp., *Eubacterium* spp., and *Peptostreptococcus* spp.. For *Bacteroides fragilis* there was an increase. These changes returned to normal within two weeks.

Mechanism of resistance
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 (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also effect susceptibility to moxifloxacin.
*In vitro* resistance to moxifloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Moxifloxacin is a poor substrate for active efflux mechanisms in Gram-positive organisms.
Cross-resistance is observed with other fluoroquinolones. However, as moxifloxacin inhibits both topoisomerase II and IV with similar activity in some Gram-positive bacteria, such bacteria may be resistant to other quinolones, but susceptible to moxifloxacin.

In vitro Susceptibility Data

EUCAST clinical MIC breakpoints for moxifloxacin (31.01.2006):

| **Organism** | **Susceptible** | **Resistant** |
|---|---|---|
| *Staphylococcus* spp. | ≤ 0.5 mg/l | > 1 mg/l |
| *S. pneumoniae* | ≤ 0.5 mg/l | > 0.5 mg/l |
| *Streptococcus* Groups A, B, C, G | ≤ 0.5 mg/l | > 1 mg/l |
| *H. influenzae* and *M. catarrhalis* | ≤ 0.5 mg/l | > 0.5 mg/l |
| *Enterobacteriaceae* | ≤ 0.5 mg/l | > 1 mg/l |
| Non-species related breakpoints* | ≤ 0.5 mg/l | > 1 mg/l |
| * Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined (Gram-negative anaerobes). | | |

Clinical and Laboratory Standards Institute™ (CLSI), formerly NCCLS breakpoints are presented in the below table for MIC testing (mg/l) or disc diffusion testing (zone diameter [mm]) using a 5-µg moxifloxacin disc.

Clinical and Laboratory Standards Institute™ (CLSI) MIC and disc diffusion breakpoints for *Staphylococcus* spp. and fastidious organisms (M100-S17, 2007) and MIC breakpoints for anaerobes (M11-A7, 2007):

| **Organism** | **Susceptible** | **Intermediate** | **Resistant** |
|---|---|---|---|
| *S. pneumoniae* | ≤ 1 mg/l<br>≥ 18 mm | 2 mg/l<br>15 - 17 mm | ≥ 4 mg/l<br>≤ 14 mm |
| *Haemophilus* spp. | ≤ 1 mg/l<br>≥ 18 mm | -<br>- | -<br>- |
| *Staphylococcus* spp. | ≤ 0.5 mg/l<br>≥ 24 mm | 1 mg/l<br>21 - 23 mm | ≥ 2 mg/l<br>≤ 20 mm |
| Anaerobes | ≤ 2 mg/l | 4 mg/l | ≥ 8 mg/l |

The prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that utility of the agent in at least some types of infections is questionable.

| **Commonly susceptible species** |
|---|
| Aerobic Gram-positive micro-organisms<br>*Gardnerella vaginalis*<br>*Staphylococcus aureus** (methicillin-susceptible)<br>*Streptococcus agalactiae* (Group B)<br>*Streptococcus milleri* group* (*S. anginosus, S. constellatus and S. intermedius*)<br>*Streptococcus pneumoniae**<br>*Streptococcus pyogenes** (Group A) |
| Aerobic Gram-negative micro-organisms<br>*Haemophilus influenzae**<br>*Haemophilus parainfluenzae**<br>*Klebsiella pneumoniae**[#]<br>*Moraxella (Branhamella) catarrhalis** |
| Anaerobic micro-organisms<br>*Fusobacterium* spp.<br>*Peptostreptococcus* spp.<br>*Prevotella* spp. |
| "Other" micro-organisms<br>*Chlamydophila (Chlamydia) pneumoniae**<br>*Chlamydia trachomatis**<br>*Coxiella burnetii*<br>*Legionella pneumophila*<br>*Mycoplasma genitalium*<br>*Mycoplasma hominis*<br>*Mycoplasma pneumoniae** |
| **Species for which acquired resistance may be a problem** |
| Aerobic Gram-positive micro-organisms<br>*Staphylococcus aureus* (methicillin-resistant)[+] |
| Aerobic Gram-negative micro-organisms<br>*Enterobacter cloacae**<br>*Escherichia coli**<br>*Klebsiella oxytoca*<br>*Neisseria gonorrhoeae**[+] |
| **Inherently resistant organisms** |
| Aerobic Gram-negative micro-organisms<br>*Pseudomonas aeruginosa* |
| *Activity has been satisfactorily demonstrated in susceptible strains in clinical studies in the approved clinical indications.<br>[#]ESBL-producing strains are commonly resistant to fluoroquinolones<br>[+]Resistance rate > 50% in one or more countries |

## 5.2 Pharmacokinetic properties

Absorption and Bioavailability
Following oral administration moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 91%.

Pharmacokinetics are linear in the range of 50 - 800 mg single dose and up to 600 mg once daily dosing over 10 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 h post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively. At steady-state the exposure within the dosing interval is approximately 30% higher than after the first dose.

Distribution
Moxifloxacin is distributed to extravascular spaces rapidly; after a dose of 400 mg an AUC of 35 m·gh/l is observed. The steady-state volume of distribution (Vss) is approximately 2 l/kg. *In vitro* and *ex vivo* experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

The following peak concentrations (geometric mean) were observed following administration of a single oral dose of 400 mg moxifloxacin:

| Tissue | Concentration | Site: Plasma ratio |
|---|---|---|
| Plasma | 3.1 mg/l | - |
| Saliva | 3.6 mg/l | 0.75 - 1.3 |
| Blister fluid | 1.6[1] mg/l | 1.7[1] |
| Bronchial mucosa | 5.4 mg/kg | 1.7 - 2.1 |
| Alveolar macrophages | 56.7 mg/kg | 18.6 - 70.0 |
| Epithelial lining fluid | 20.7 mg/l | 5 - 7 |
| Maxillary sinus | 7.5 mg/kg | 2.0 |
| Ethmoid sinus | 8.2 mg/kg | 2.1 |
| Nasal polyps | 9.1 mg/kg | 2.6 |
| Interstitial fluid | 1.0[2] mg/l | 0.8 - 1.4[2,3] |
| Female genital tract* | 10.2[4] mg/kg | 1.72[4] |

* intravenous administration of a single 400 mg dose
[1] 10 h after administration
[2] unbound concentration
[3] from 3 h up to 36 h post dose
[4] at the end of infusion

Metabolism
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

In clinical Phase I and *in vitro* studies no metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes were observed. There is no indication of oxidative metabolism.

Elimination
Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys.

After a 400 mg dose, recovery from urine (approximately 19% for unchanged drug, approximately 2.5% for M1, and approximately 14% for M2) and faeces (approximately 25% of unchanged drug, approximately 36% for M1, and no recovery for M2) totalled to approximately 96%.

Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

Higher plasma concentrations are observed in healthy volunteers with low body weight (such as women) and in elderly volunteers.

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance > 20 ml/min/1.73 $m^2$). As renal function decreases,

concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 $m^2$).

On the basis of the pharmacokinetic studies carried out so far in patients with liver failure (Child Pugh A, B), it is not possible to determine whether there are any differences compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas exposure to parent drug was comparable to exposure in healthy volunteers. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

**PACKAGE LEAFLET**

## 1. WHAT [INVENTED NAME] 400 MG FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

[Invented name] is an antibiotic belonging to the quinolone family. [Invented name] contains moxifloxacin as the active ingredient which belongs to a group of antibiotics called fluoroquinolones. [Invented name] works by killing bacteria that cause infections, if they are caused by bacteria that are susceptible to the active ingredient moxifloxacin.

[Invented name] is used in adults for treating the following bacterial infections:
- Sudden worsening of chronic bronchitis (acute exacerbation of chronic bronchitis)
- Infection of the lungs (pneumonia) acquired outside the hospital, except severe cases
- Acute infection of the sinuses (acute bacterial sinusitis)
- 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. [Invented name] tablets are not sufficient for sole therapy of this kind of infections and therefore another antibiotic in addition to [Invented name] tablets should be prescribed by your doctor for the treatment of infections of the female upper genital tract (see section *2. Before you take [Invented name] …, Take special care …, Before taking [Invented name] 400 mg film-coated tablets*).

## 2. BEFORE YOU TAKE [INVENTED NAME] 400 MG FILM-COATED TABLETS

Contact your doctor if you are not sure if you belong to a patient group described below.

**Do not take [Invented name] 400 mg film-coated tablets**
- If you are allergic (hypersensitive) to the active ingredient moxifloxacin, any other quinolone antibiotics or any of the other ingredients (see section 6. *Further information*) of [Invented name] 400 mg film-coated tablets.
- If you are pregnant or breast-feeding.
- If you are under 18 years of age.
- If you have a history of tendon disease or disorder which was related to treatment with quinolone antibiotics (see sections *Take special care ...* and *4. Possible side effects*).
- If you were born with or have had any condition with certain abnormal electrocardiogram (ECG, electrical recording of the heart) changes,
  have salt imbalance in the blood, especially low concentrations of potassium in the blood (hypokalaemia) which are currently not corrected by treatment,
  have a very slow heart rate (bradycardia),
  have a weak heart (heart failure),
  have a history of abnormal heart rhythms (arrhythmias),
  or you are taking other medicines that result in certain abnormal ECG changes (see section *Taking other medicines*).
  This is because [Invented name] can cause a certain change on the ECG, that is a prolongation of the QT-interval i.e delayed conduction of electrical signals.
- If you have a severe liver disease or increased liver enzymes (transaminases) higher than 5 times the upper normal limit.

**Take special care with [Invented name] 400 mg film-coated tablets**

**Before taking [Invented name] 400 mg film-coated tablets**
- [Invented name] can change your heart's ECG. If you are currently taking any medicine that decrease your blood potassium levels, consult your doctor before taking [Invented name]. 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.
- If you suffer from epilepsy or a condition which makes you likely to have convulsions, consult your doctor before taking [Invented name].

- If you or any member of your family have glucose-6-phosphate dehydrogenase deficiency (a rare hereditary disease), inform your doctor, who will advise whether [Invented name] is suitable for you.
- If you have a complicated infection of the female upper genital tract (e.g. associated with an abscess of the fallopian tubes and ovaries or of the pelvis), for which your doctor considers an intravenous treatment necessary, treatment with [Invented name] tablets is not appropriate.
- For the treatment of mild to moderate infections of the female upper genital tract your doctor should prescribe another antibiotic in addition to [Invented name]. If there is no improvement in symptoms after 3 days of treatment, please consult your doctor.

**When taking [Invented name] 400 mg film-coated tablets**
- The risk of cardiac abnormalities may increase with increase of the dose. Therefore, you should adhere to the dosage.
- There is a rare chance that you may experience a severe, sudden allergic reaction (an anaphylactic reaction/shock) even with the first dose, with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. If so, stop taking [Invented name] and seek medical advice immediately.
- [Invented name] may cause a rapid and severe inflammation of the liver which could lead to life-threatening liver failure (see section *4. Possible side effects*). Please contact your doctor before you continue the treatment if you develop signs such as rapidly feeling unwell and/or being sick associated with yellowing of the whites of the eyes, dark urine, itching of the skin, a tendency to bleed or liver induced disease of the brain (symptoms of a reduced liver function or a rapid and severe inflammation of the liver).
- You may develop diarrhoea whilst taking, or after taking, antibiotics including [Invented name]. If this becomes severe or persistent or you notice that your stool contains blood or mucus you should stop taking [Invented name] immediately and consult your doctor. In this situation, you should not take medicines that stop or slow down bowel movement.
- [Invented name] may occasionally cause pain and inflammation of your tendons, particularly if you are elderly or if you are currently being treated with corticosteroids. At the first sign of any pain or inflammation you should stop taking [Invented name], rest the affected limb and consult your doctor immediately.
- If you are elderly with existing kidney problems take care that your fluid intake is sufficient because dehydration may increase the risk of kidney failure.
- If your eyesight becomes impaired or if you have any other eye disturbances whilst taking [Invented name], consult an eye specialist immediately.
- Quinolone antibiotics may make your skin become more sensitive to sunlight or UV light. You should avoid prolonged exposure to sunlight or strong sunlight and should not use a sunbed or any other UV lamp while taking [Invented name].

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines besides [Invented name], including medicines obtained without a prescription.
For [Invented name] be aware of the following:
- If you are taking [Invented name] and other <u>medicines that affect your heart</u> there is an increased risk for altering your heartbeat. Therefore, do not take [Invented name] together with the following medicines: Medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), neuroleptics (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).
- Any <u>medicine containing magnesium or aluminium</u> such as antacids for indigestion, or any <u>medicine containing iron or zinc</u>, <u>medicine containing didanosine</u> or <u>medicine containing sucralfate to treat gastrointestinal disorders</u> can reduce the action of [Invented name] tablets. Therefore, take your [Invented name] tablet 6 hours before or after taking the other medicine.
- Taking <u>oral medicinal charcoal</u> at the same time as [Invented name] tablets reduces the action of [Invented name]. Therefore it is recommended that these medicines are not used together.

- If you are currently taking oral anti-coagulants (e.g. warfarin), it may be necessary for your doctor to monitor your blood clotting times.

**Taking [Invented name] 400 mg film-coated tablets with food and drink**
The effect of [Invented name] is not influenced by food including dairy products.

**Pregnancy and breast-feeding**
Do not take [Invented name] if you are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
[Invented name] may make you feel dizzy or light-headed. If you are affected in this way do not drive or operate machinery.

**Important information about some of the ingredients of [Invented name] 400 mg film-coated tablets**
[Invented name] tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking [Invented name].

## 3. HOW TO TAKE [INVENTED NAME] 400 MG FILM-COATED TABLETS

Always take [Invented name] exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure how to take [Invented name].

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

[Invented name] tablets are for oral use. Swallow the tablet as a whole (to mask the bitter taste) and with plenty of liquid. You can take [Invented name] with or without food. It is recommended that you take the tablet at approximately the same time each day.

No adjustment of the dose is required in elderly patients, patients with a low bodyweight or in patients with kidney problems.

The duration of treatment depends upon the type of infection. Unless otherwise indicated by your doctor the recommended durations of use of [Invented name] are:
- Sudden worsening of chronic bronchitis (acute exacerbation of chronic bronchitis) 5 - 10 days
- Infection of the lungs acquired (pneumonia) outside the hospital, except severe cases 10 days
- Acute infection of the sinuses (acute bacterial sinusitis) 7 days
- 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

It is important that you complete the course of treatment, even if you begin to feel better after a few days. If you stop taking this medicine too soon your infection may not be completely cured, the infection may return or your condition may get worse, and you may also create a bacterial resistance to the antibiotic.

The recommended dose and duration of treatment should not be exceeded (see section *2. Before you take [Invented name] ...*, *Take special care ...*).

**If you take more [Invented name] 400 mg film-coated tablets than you should**

If you take more than the prescribed one tablet a day, seek medical advice immediately and, if possible, take any remaining tablets, the packaging or this leaflet with you to show the doctor or pharmacist what you have taken.

**If you forget to take [Invented name] 400 mg film-coated tablets**
If you forget to take your tablet you should take it as soon as you remember on the same day. If you do not take your tablet on one day, take your normal dose (one tablet) on the next day. Do not take a double dose to make up for a forgotten dose.
If you are unsure about what to do, consult your doctor or pharmacist.

**If you stop taking [Invented name] 400 mg film-coated tablets**
If you stop taking this medicine too soon your infection may not be completely cured. Consult your doctor if you wish to stop taking your tablets before the end of the course of treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.