ANNEX II

THE SCIENTIFIC CONCLUSIONS AND THE GROUNDS FOR AMENDMENTS OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ORAL FORMULATIONS OF MOXIFLOXACIN CONTAINING MEDICINAL PRODUCTS (see Annex I)

Moxifloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. In the European Union (EU), Moxifloxacin film coated tablet are indicated for the treatment of acute bacterial sinusitis (ABS), acute exacerbation of chronic bronchitis (AECB) and community acquired pneumonia (CAP) except severe cases, at the dose of 400 mg daily for 7 days for ABS, 5-10 days for AECB and for 10 days for CAP. In the EU, moxifloxacin is authorised in all Member States, via the Mutual Recognition or National Procedure.

Severe hepatotoxicity, cardiac toxicity including QTc interval prolongation, severe skin reactions, *Clostridium difficile* associated colitis, tendon and muscular toxicity (including rhabdomyolysis) are important identified risks of the treatment with moxifloxacin which are already described in the product information (PI) and under close monitoring.

In October 2007, the assessment of the 15th and 16th PSUR for moxifloxacin identified major safety concerns including life threatening hepatotoxicity cases. A cumulative review up to 30 September 2007 of all hepatic reactions (serious and non-serious) and an overall assessment of the benefit/risk ratio of moxifloxacin treatment was performed.

Of a total of 48 identified cases of possibly moxifloxacin-related liver disorders with a fatal outcome of any cause, 8 were suspected cases of moxifloxacin-induced fatal hepatotoxicity. In 3 of these, moxifloxacin was used for treating less severe indications (sinusitis, pharyngitis and acute bronchitis).

These findings and additional available data (observational study and clinical trials) suggested that serious liver injuries occurred more frequently with moxifloxacin then with the comparators.

Based on the above, on 2 June 2008, the UK issued a Rapid Alert informing Members States, the European Medicines Agency (EMEA) and the European Commission (EC) in accordance with Article 107 of Directive 2001/83/EC, as amended of its intention to vary the marketing authorisation of all oral formulations of moxifloxacin containing medicinal products to remove the indications in ABS and AECB and to restrict the indication in CAP.

The CHMP reviewed all of the information made available by marketing authorisation holders (MAH) on the balance of benefits and risks of oral moxifloxacin in the above indications.

Moxifloxacin has shown efficacy in all of the approved indications. Notwithstanding this fact, the safety profile of the product is of concern.

The CHMP noted:

ABS
ABS is generally a non-severe infection associated with high spontaneous cure rates (90%). A substantial proportion of prescriptions for sinusitis in clinical practice may be empirical and without confirmation of bacterial origin. Although moxifloxacin has shown to be effective, the available data is limited as studies have been mainly performed against comparators and the only placebo controlled study failed to demonstrate statistical superiority over placebo. Considering the higher incidence of serious and even life-threatening risks in the treatment of an infection which has a high spontaneous resolution rate without antibiotics was considered of concern. However, the benefit risk of moxifloxacin may be favourable if other antibiotherapy has failed or cannot be used.

AECB
The benefit of antibiotic treatment of AECB was supported by several publications including a meta-analysis and by a recent systematic review from Cochrane Centre suggesting a mortality benefit with the use of antibiotics in this indication in comparison with placebo and a beneficial effect on lung function. However, it was noted that until recently antibiotic comparative trials in AECB designed to

show equivalence between medicinal products did not demonstrate clinical superiority of any class of antibiotics over another. Additionally, most of the phase III studies designed for non-inferiority for moxifloxacin did not use the recommended agent of choice. Therefore, since the impact of the choice of an antibiotic therapy for AECB on the outcome of the patients remains unclear, the safety profile of the different antibiotherapy options must be considered. In line with the safety profile, and considering that AECB can be a less severe infection, with high spontaneous resolution rate for which bacteria can be found in only 50% of all exacerbations, the benefit risk can only be considered favourable if moxifloxacin is not used as the first line treatment option.

CAP

Clinical trial and published data indicate that moxifloxacin generally has benefits in the indication CAP. Furthermore, when taking into account other antiobiotherapy available and resistance, some times advantages over other therapies are observed in the treatment of CAP of mild to moderate severity. However, considering the safety profile with observed increased incidence of risks, moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection.

In view of the above, the CHMP recommended the restriction to 2nd line treatment in the indications for moxifloxacin containing medicinal products (oral formulation) and further amendments to the PI, to include fatal hepatotoxicity cases, risk factors for QTc interval prolongation, and strengthen the warnings on *Clostridium difficille*-associated colitis and bullous skin reactions.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS

Whereas,

The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing moxifloxacin in oral formulations.

In view of the available data the Committee concluded that the benefit risk balance of moxifloxacin containing medicinal products in oral formulations in the approved indications under review is favourable as second line indications. In ABS and AECB, moxifloxacin should only be used 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 to resolve the infection. In CAP, it is to be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection.

In view of the safety available data the Committee concluded that cases of fatal hepatotoxicity, risk factors for QTc interval prolongation should be reflected in the product information, and that the warnings on *Clostridium difficille*-associated colitis and bullous skin reactions should be strengthen.

The CHMP, as a consequence recommended amendments to the relevant sections of the summary of product characteristics and package leaflet for the medicinal products containing moxifloxacin (see Annex III).