Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for moxifloxacin (systemic use), the scientific conclusions are as follows:

Cumulatively, there were 58 cases of vasculitis (37 cases of vasculitis, 18 cases of hypersensitivity vasculitis 2 cases of "cutaneous vasculitis" and one case of urticarial vasculitis) including 13 cases reported during the reporting period of the PSUR. The most plausible biological mechanism, by which moxifloxacin and other fluoroquinolones may trigger vasculitis and hypersensitivity vasculitis, is by immune complex formation. Vasculitis as a clinical manifestation of hypersensitivity reactions is also labelled in the EU as adverse reaction for several other fluoroquinolones. Based on the information presented in this PSUR, PRAC considered that vasculitis should be added to sections 4.8 as well as section 4.4 of the product information with regard to hypersensitivity reactions.

There were 50 reports of peripheral neuropathy. In 12 cases causality couldn't be discarded. Although the available data may be inconclusive with regards to the irreversibility of the reactions, relevant information over the long-term follow-up was lacking. It can therefore not be excluded that there may be individual case reports with irreversible outcome. Based on the information reviewed in this PSUR, PRAC considered that section 4.4 of the SmPC should be amended. Additionally, PRAC considered that information for patients regarding the location of symptoms should be added.

Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products containing moxifloxacin (systemic use) were warranted.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for moxifloxacin (systemic use) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing moxifloxacin (systemic use) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing moxifloxacin (systemic use) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

The following warnings should be revised as follows:

Hypersensitivity/allergic reactions

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 cases **of clinical manifestations of severe hypersensitivity reactions** moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop **in order to prevent the development of an irreversible condition** (see section 4.8).

- Section 4.8

The following paragraph of section 4.8 should be modified as follows:

Adverse reactions observed in clinical trials **and derived from post-marketing reports** with [moxifloxacin systemic use]:

The following adverse reaction(s) should be added under the SOC Vascular disorders with a frequency very rare as follows:

vasculitis

Package Leaflet

- Section 2

…

You may experience symptoms of **nerve damage (**neuropathy**)** such as pain, burning, tingling, numbness and/or weakness **especially in the feet and legs or hands and arms**. If this happens, inform your doctor immediately prior to continuing treatment with <product name>.

- Section 4

The following adverse reaction(s) should be added to the paragraph on adverse reactions for which urgent action is needed (stop taking X and tell your doctor immediately as you may need urgent medical advice.)

- alterations of the skin and mucous membranes like painful blisters in the mouth/nose or at the penis/vagina (Stevens-Johnson syndrome or toxic epidermal necrolysis) (very rare side effects, potentially life threatening)

- **Inflammation of blood vessels (signs could be red spots on your skin, usually on your lower legs or effects like joint pain) (very rare side effect)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 May 2017