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:

In view of available data on DRESS from the literature, spontaneous reports including in some cases a close temporal relationship and a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between moxifloxacin (systemic use) and DRESS is at least a reasonable possibility.

In view of available data on fixed drug eruption from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and re-challenge, the PRAC considers a causal relationship between moxifloxacin (systemic use) and fixed drug eruption is at least a reasonable possibility.

In view of available data on photosensitivity reactions from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between moxifloxacin (systemic use) and photosensitivity reactions is at least a reasonable possibility.

The PRAC concluded that the product information of products containing moxifloxacin (systemic use) should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

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 recommends that the terms of the marketing authorisation(s) should be varied.

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

Warnings should be amended as follows:

[…]

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS)**,** ~~and~~ Acute Generalised Exanthematous Pustulosis (AGEP) **and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**, which could be life-threatening or fatal, have been reported with moxifloxacin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, moxifloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN**,** ~~or~~ AGEP **or DRESS** with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.

[…]

Prevention of photosensitivity reactions

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 **(see section 4.8)**.

- Section 4.8

The following adverse reactions should be added within the table of ADRs under the SOC Skin and subcutaneous tissue disorders with a frequency not known:

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption, Photosensitivity reactions (see section 4.4)

[…]

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia**.**~~, photosensitivity reactions (see section 4.4).~~

Package Leaflet

Section 2. What you need to know before you take moxifloxacin

[…]

When taking moxifloxacin

[…]

- **Serious skin reactions**

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, ~~and~~ acute generalised exanthematous pustulosis (AGEP) **and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)** have been reported with the use of moxifloxacin.

- SJS/TEN can appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious skin rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications or be fatal.
- AGEP appears at the initiation of treatment as a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The most common location: mainly localized on the skin folds, trunk, and upper extremities.
- **DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high body temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.**

If you develop a serious rash or another of these skin symptoms, stop taking moxifloxacin and contact your doctor or seek medical attention 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 [product name] **(see section 4. Possible side effects)**.

[…]

Section 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The **most serious side effects** observed during the treatment with moxifloxacin are listed below:

If you notice

[…]

- A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis) (frequency of this side effect is ‘not known’)
- **Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (drug reaction with eosinophilia and systemic symptoms which is also known as DRESS or drug hypersensitivity syndrome) (frequency of this side effect is ‘not known’).**

[…]

Other side effects which have been observed during treatment with [product name] are listed below by how likely they are:

[…]

Not known (frequency cannot be estimated from the available data)

- **Increased sensitivity of the skin to sunlight or UV light (see also section 2, Warnings and precautions).**

- **<u>Sharply demarcated, erythematous patches with/without blistering that develop within hours of administration of moxifloxacin and heals with post inflammatory residual hyperpigmentation; it usually recurs at the same site of the skin or mucous membrane upon subsequent exposure to moxifloxacin</u>**

[…]

Furthermore, there have been very rare cases of the following side effects reported following treatment with other quinolone antibiotics, which might possibly also occur during treatment with [product name]: raised pressure in the skull (symptoms include headache, visual problems including blurred vision, "blind" spots, double vision, loss of vision), increased blood sodium levels, increased blood calcium levels, a special type of reduced red blood cell count (haemolytic anaemia).~~, increased sensitivity of the skin to sunlight or UV light.~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 March 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09 May 2024