# 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:

- Pancytopenia:

  Out of the 32 post-marketing cases identified cumulatively in the MAH's safety database, 1 case with positive dechallenge is considered by the LMS to be probably causally associated with moxifloxacin and 19 cases possibly; in 7 of these 19 cases a positive dechallenge was recognizable. For 2 of the 3 cases from clinical trials the causal association is considered at least suspected by the LMS. Pancytopenia is a listed ADR in section 4.8 of the SmPC of ciprofloxacin, levofloxacin and ofloxacin. An update of the product information (SmPC section 4.8 and PL section 4) to reflect pancytopenia as ADR with frequency 'very rare' in accordance with the SmPC guideline is warranted.

- AGEP:

  Out of the 5 post-marketing reports identified cumulatively in the MAH's safety database and literature, 3 are considered probably causally associated with moxifloxacin and 1 possibly. In 2 of the 3 cases with probable causal association, AGEP resolved after discontinuation of moxifloxacin plus corrective therapy and in the 3rd a positive rechallenge was recorded. No cases were reported from clinical trials. AGEP is currently listed as an ADR in section 4.8 of the SmPC of both ciprofloxacin and ofloxacin. An update of the the SmPC sections 4.4 and 4.8 and the respective section of the PL to reflect AGEP in line with the wording recommended by SCARs Guidance and with frequency 'not known' is justified.

- Hypoglycaemic coma:

  Out of the 8 post-marketing cases identified cumulatively in the MAH's safety database, 6 are considered by the LMS to be possibly causally associated with moxifloxacin. Two of these 6 cases ended fatally and hypoglycaemic coma was considered by the respective reporting HCP as one cause of death in each case and as related to moxifloxacin use. In both cases diabetes was not reported as concurrent condition. The causal association in one of the 2 cases identified from clinical trials is considered at least suspected by the LMS. In frame of the last PSUSA for ciprofloxacin (systemic use), PRAC and CMDh recommended an update of SmPC sections 4.4 and 4.8 to reflect hypoglycaemic coma, which is also reflected in SmPC sections 4.4 and 4.8 and respective sections of the PL of both levofloxacin and ofloxacin. An update of the product information (SmPC section 4.8 and PL sections 2 and 4) to reflect hypoglycaemic coma as ADR with frequency 'very rare' in accordance with the SmPC guideline is warranted.

- Delirium:

  Out of the 369 cases of delirium identified cumulatively in the MAH's safety database, 30 medically confirmed and serious cases were considered by the MAH to not show alternative explanation. The LMS considers a reasobale time relationship for all 30 cases. In 5 of these 30 cases a positive dechallenge was recorded: in 3 of these cases the causal association is considered probable, while in the remaining two possible. In four additional post-marketing cases from literature the causal association is considered possible. Recently and in frame of the worksharing procedure for levofloxacin and ofloxacin, delirium was recommended to be labelled as an ADR in section 4.8 of the respective SmPC. An update of the SmPC section 4.8 to reflect delirium as ADR with frequency 'rare' in accordance with the SmPC guideline is warranted.

- SIADH:

  Out of the 5 reports (1 clinical trial case and 4 from post-marketing) identified cumulatively in

the MAH's safety database, 1 post-marketing case is considered by the LMS of probable causal association, while in the remaining 3 post-marketing cases possible. In one of the 4 cases a positive dechallenge was recorded and in the remaining 3 SIADH resolved after discontinuation of moxifloxacin plus corrective therapy with saline solutions. The causal association in the case from clinical trials can't be excluded. In frame of the last PSUSA for ciprofloxacin (systemic use) and for levofloxacin (except for the centrally authorised product), PRAC and CMDh recommended the update of the product information of ciprofloxacin and respectively levofloxacin to reflect SIADH as ADR. An update of the product information (SmPC section 4.8 and PL section 4) to reflect SIADH as ADR with frequency 'very rare' in accordance with the SmPC guideline is warranted.

- Rhabdomyolysis:

  Out of the 40 post-marketing reports identified cumulatively in the MAH's safety database, 35 are considered by the LMS to show a reasonable time relationship. One of these 35 cases is probably causally associated with moxifloxacin and 34 possibly. In 8 of the 35 cases a positive dechallenge was recorded and in one of them also a positive rechallenge with garenoxacin. Rhabdomyolysis is already labelled as an ADR in section 4.8 of the SmPC of levofloxacin, ofloxacin and norfloxacin. The wording in the product information of moxifloxacin does not reflect the current evidence as it states that rhabdomyolysis was only reported for „other fluoroquinolones" (section 4.8). Therefore, the product information (SmPC section 4.8 and PL section 4) should be updated in order to present rhabdomyolysis as a possible ADR of moxifloxacin with frequency 'not known'.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing moxifloxacin for 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 the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

# 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**

~~Serious bullous skin reactions~~

~~Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.~~

**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), 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 with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.**

- **Section 4.8**

SOC Blood and Lymphatic System Disorders

Frequency: very rare

**Pancytopenia**

SOC Endocrine disorders

Frequency: very rare

**Syndrome of inappropriate antidiuretic hormone secretion (SIADH)**

SOC Metabolism and Nutrition Disorders

Frequency: very rare

**Hypoglycaemic coma**

SOC Psychiatric Disorders

Frequency: rare

**Delirium**

Skin and Subcutaneous Tissue Disorders

Frequency: 'not known'

**Acute Generalised Exanthematous Pustulosis (AGEP)**

SOC Musculoskeletal and connective tissue disorders

Frequency: 'not known'

**Rhabdomyolysis**

**[…]**

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, ~~rhabdomyolysis,~~ photosensitivity reactions (see section 4.4).

**Package Leaflet**

**Section 2**

**Warnings and precautions**

**Before taking this medicine**

You should not take fluoroquinolone/quinolone antibacterial medicines, including [product name], if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

**Talk to your doctor before taking moxifloxacin**

- **If you are diabetic because you may experience a risk of change in blood sugar levels with moxifloxacin.**
- **If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking moxifloxacin.**

**When taking moxifloxacin**

- ~~If you develop a skin reaction or blistering / peeling of the skin and/or mucosal reactions (see section 4. Possible side effects) contact your doctor immediately before you continue treatment.~~

**Serious skin reactions**

**Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalised exanthematous pustulosis (AGEP) 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.**

**If you develop a serious rash or another of these skin symptoms, stop taking moxifloxacin and contact your doctor or seek medical attention immediately.**

**[…]**

- Fluoroquinolone antibiotics may cause ~~disturbances in blood sugar, including both a decrease in blood sugar below normal levels (hypoglycemia) and~~ an increase **of your** ~~in~~ blood sugar **levels** above normal levels (hyperglycaemia)**, or lowering of your blood sugar levels below normal levels (hypoglycaemia), potentially leading to loss of consciousness** ~~(see section 4. Possible side effects). In patients treated with [product name], disturbances in blood sugar occurred predominantly in elderly diabetic patients receiving concomitant treatment with oral antidiabetic medicines that lower blood sugar (e. g. sulfonylurea) or with insulin. Loss of consciousness due to severe reduction in blood sugar~~ (hypoglycaemic coma) **in severe cases (see section 4. Possible side effects)** ~~have been reported~~. If you suffer from diabetes, your blood sugar should be carefully monitored.

**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 [product name] are listed below:

If you notice

[…]

- ~~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)~~
- **Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms (very rare side effects, potentially life threatening)**
- **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')**
- **Syndrome associated with impaired water excretion and low levels of sodium (SIADH) (very rare side effect)**
- **Loss of consciousness due to severe decrease in blood sugar levels (hypoglycaemic coma) (very rare side effect)**

[…]

- pain and swelling of the tendons (tendonitis) (rare side effect) or a tendon rupture (very rare side effect)

- **muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis) (frequency of this side effect is 'not known')**

[…]

Other side effects which have been observed during treatment with moxifloxacin are listed below by how likely they are:

**Very rare** (may affect up to 1 in 10,000 people) […]

- **a drop in the number of red and white blood cells and platelets (pancytopenia)**

[..]

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), ~~muscle reactions with muscle cell damage,~~ 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**

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|---|---|
| Adoption of CMDh position: | January /2020 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 15/03/2020 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 14/05/2020 |