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 levofloxacin (intravenous and oral use), the scientific conclusions are as follows:

In view of available data on bone marrow failure, myoclonus, mania and skin hyperpigmentation from the literature and spontaneous reports including in some cases a close temporal relationship, a positive dechallenge and/or rechallenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between levofloxacin (intravenous and oral use) and bone marrow failure, myoclonus, mania and skin hyperpigmentation is at least a reasonable possibility. The PRAC concluded that the product information of products containing levofloxacin (intravenous and oral 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 levofloxacin (intravenous and oral use) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levofloxacin (intravenous and oral 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 added as follows:

[...]
Tendinitis and tendon rupture

[…]

Myoclonus

Cases of myoclonus have been reported in patients receiving levofloxacin (see section 4.8). The risk of myoclonus is increased in older patients, and in patients with renal impairment if the dose of levofloxacin is not adjusted as per the creatinine clearance. Levofloxacin should be discontinued immediately at the first occurrence of myoclonus and appropriate treatment should be initiated.

[...]
Acute pancreatitis

[…]

Blood disorders

Bone marrow failure including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia, or agranulocytosis may develop during treatment with levofloxacin (see section 4.8). If any of these blood disorders is suspected, blood counts should be monitored. In case of abnormal results, discontinuation of treatment with levofloxacin should be considered.

- Section 4.8

The following adverse reaction(s) should be added or amended:

Under the SOC Blood and lymphatic system disorders:

Frequency Not known (cannot be estimated from available data): Bone marrow failure including aplastic anaemia, ~~P~~**p**ancytopenia**,** ~~A~~**a**granulocytosis**,** ~~H~~**h**aemolytic anaemia

Under the SOC Psychiatric disorders

Frequency Not known: [...] Mania

Under the SOC Nervous system disorders

Frequency Not known: [...] Myoclonus

Under the SOC Skin and subcutaneous tissue disorders

Frequency Not known (cannot be estimated from available data): […] Skin hyperpigmentation

- Section 4.9

The signs of overdose should be amended as follows:

[…]

CNS effects including confusional state, convulsion, **myoclonus,** hallucination, and tremor have been observed in post marketing experience.

Package Leaflet

Section 2

[…]

Warnings and precautions

[…]

when you are taking your medicine :

[…]

- **If you start experiencing sudden involuntary jerks, twitches of the muscles or muscle contractions - see a doctor straight away as this could be signs of myoclonus. Your doctor may need to stop treatment with levofloxacin and to start an appropriate treatment.**
- If you are having nausea, feeling generally unwell, have severe discomfort or on-going pain or worsening pain in the stomach area or vomiting – see a doctor straight away, as this could be a sign of an inflamed pancreas (acute pancreatitis).
- **If you are experiencing fatigue, skin pale, bruising, uncontrolled bleeding, fever, sore throat and serious deterioration of your general condition, or a feeling that your resistance to infection may be decreased - see a doctor straight away as this could be signs of blood disorders. Your doctor should monitor your blood with blood counts. In case of abnormal blood counts, your doctor may need to stop treatment.**

Section 4

[…]

Tell your doctor if any of the following side effects gets serious or lasts longer than a few days:

[…]

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

- Lowering in red blood cells (anemia): this can make the skin pale or yellow due to damage of the red blood cells; lowering in the number of all types of blood cells (pancytopenia)
- **Bone marrow stops producing new blood cells, this may cause tiredness, lower ability**

to fight infection and uncontrolled bleeding (bone marrow failure)
[…]

- Changes in the way things smell, loss of smell or taste (parosmia, anosmia, ageusia)
- **Feeling very excited, elated, agitated or enthusiastic (mania)**
  […]
- Increased sensitivity of your skin to sun and ultraviolet light (photosensitivity), **darker areas of skin (hyperpigmentation)**

  […]
- Pain, including pain in the back, chest and extremities

Sudden involuntary jerks, twitches of the muscles or muscle contractions (myoclonus)

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	May, 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	14 July 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 September 2024