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 (except for the centrally authorised product) the scientific conclusions are as follows:

Levofloxacin for systemic use (ATC code J01MA12)

- DRESS: From data on summary tabulations, a constant accumulation of cases of DRESS is recognizable on levofloxacin use. Two well-documented literature cases of DRESS were assessed by the LMS to be probable causally associated with levofloxacin use as the time to onset is compatible, positive dechallenge was recorded, and DRESS is unlikely to be attributed to other drugs. Moreover, out of the 72 cases related to DRESS identified in the safety database of the MAHs, 58 cases of DRESS were assessed by the LMS to be possible causally related to levofloxacin mainly due to a compatible time to onset. DRESS is reflected in the product information (SmPC and PL) from other fluoroquinolones, namely ciprofloxacin and norfloxacin, in both with a frequency "unknown". An update of the product information (SmPC and PL) of levofloxacin for systemic use to reflect DRESS in line with the wording recommended by SCARs Guidance is warranted. Based on the the cumulative clinical trial exposure data available from the MAH Sanofi, the frequency of the event can be estimated as rare.
- SIADH: Out of the 17 cases identified in the global safety database of the MAHs, 2 well-documented cases (both with positive rechallenge) were assessed to be probable causally related to levofloxacin use and 5 possible. Additionally, the causal association of levofloxacin with the development of SIADH in 1 literature case is considered as possible. Recently and in frame of the PSUSA for ciprofloxacin for systemic use (PSUSA/00000775/201801), PRAC recommended and update of section 4.8 of the SmPC of ciprofloxacin to add the adverse reaction syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with a frequency not known and the PL will be updated accordingly. Moreover, there are published reports showing that moxifloxacin is most likely causally related to the development of SIADH. An update of the product information (SmPC and PL) of levofloxacin for systemic use to reflect SIADH is warranted. Based on the the cumulative clinical trial exposure data available from the MAH Sanofi, the frequency of the event can be estimated as rare.
- Fixed drug eruption: Out of the 28 cases with PT Drug eruption and PT Fixed eruption identified in the safety database from the MAH Terapia, the LMS considers 4 cases of Fixed drug eruption as probable causally associated with levofloxacin use (in all 4 cases a positive rechallenge was recorded), and 2 possibly. Additionally, the LMS conducted an EVDAS search using the PT Fixed eruption and identified 24 cases cumulatively. Out of them, 10 are considered by the LMS to be probable causally associated with levofloxacin use (in 7 cases a positive rechallenge was recorded), and 13 possibly. An update of the product information (SmPC and PL) of levofloxacin for systemic use to reflect fixed drug eruption is justified. Based on the the cumulative clinical trial exposure data available from the MAH Sanofi, the frequency of the event can be estimated as rare.

Levofloxacin for topical ophthalmic use (ATC code S01AE05)

Upon review of reports related to tendon disorders, a causal association of levofloxacin for topical ophthalmic use cannot be excluded at this time. Since the impact of levofloxacin for topical ophthalmic use on the vulnerable population cannot be excluded, an update of the product information emphasizing that the treatment with levofloxacin for topical ophthalmic use should be discontinued at the first sign of tendon

inflammation, as it is stated in the product information of other fluoroquinolones for topical ophthalmic use, is justified.

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 levofloxacin (except for the centrally authorised product) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levofloxacin (except for the centrally authorised product) 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 levofloxacin (except for the centrally authorised product) 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~~)

Levofloxacin for systemic use (ATC code J01MA12)

Summary of Product Characteristics

- Section 4.4

A warning should be revised as follows:

~~Severe bullous reactions~~

~~Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (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 drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin (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, levofloxacin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

- Section 4.8

The following adverse reaction(s) should be added:

SOC: Skin and subcutaneous tissue disorders

Rare: […] **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption**

SOC: **Endocrine disorders**

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

Package Leaflet

2. What you need to know before you take <product name>

Warnings and precautions

Talk to your doctor or pharmacist before taking your medicine if:

- **You have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking levofloxacin.**

[…]

Serious skin reactions

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of levofloxacin.

- **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.**
- **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 levofloxacin and contact your doctor or seek medical attention immediately.

4. Possible side effects

Rare (may affect up to 1 in 1000 people)

- **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). See also section 2.**
- **Syndrome associated with impaired water excretion and low levels of sodium (SIADH)**

[…]

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

- ~~Severe skin rashes which may include blistering or peeling of the skin around your lips, eyes, mouth, nose and genitals~~
- **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. See also section 2.**

[…]

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

Rare (may affect up to 1 in 1000 people)

[…]

Sharply demarcated, erythematous patches with/without blistering that develop within hours of administration of levofloxacin and heals with postinflammatory residual hyperpigmentation; it usually recurs at the same site of the skin or mucous membrane upon subsequent exposure to levofloxacin

Levofloxacin for topical ophthalmic use (ATC code S01AE05)

Summary of Product Characteristics

Section 4.4:

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including levofloxacin, particularly in older patients and those treated concurrently with corticosteroids. Therefore, caution should be exercised and treatment with [Product name] should be discontinued at the first sign of tendon inflammation (see section 4.8).

Section 4.8 (below the tabulated list of adverse reactions):

Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

Package Leaflet

Section 2

Warnings and precautions

Tendon swelling and rupture have happened in people taking oral or intravenous fluoroquinolones, particularly in older patients and in those treated concurrently with corticosteroids. Stop taking [Product name] if you develop pain or swelling of the tendons (tendinitis).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 July 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	6 September 2019