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 rifampicin, the scientific conclusions are as follows:

Interaction with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir, lenacapavir.

In view of available data on a pharmacokinetic interaction between rifampicin and:

- Antiviral for treatment of HCV infections - sofosbuvir,
- Antiretrovirals - cabotegravir, fostemsavir, lenacapavir
- Lurasidone

leading to significant decrease in the plasma concentrations of the interacting with rifampicin medicines, which is likely to result in loss of their therapeutic effect, PRAC concluded that the product information of products containing rifampicin should be amended accordingly.

Paradoxical drug reaction

In view of available data on paradoxical drug reaction with rifampicin from spontaneous reports and scientific literature, the PRAC considers a causal relationship between rifampicin and paradoxical drug reaction is at least a reasonable possibility. The PRAC concluded that the product information of products containing rifampicin 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 rifampicin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing rifampicin 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~~)

1. ***Interaction with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir, lenacapavir.***

If a similar or stricter wording is already included in SmPC and PL, the current wording should remain.

Summary of Product Characteristics

Section 4.3

A contraindication should be added as follows:

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir (see section 4.5).

Section 4.5

An interaction should be added as follows:

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir. Significant decrease in their plasma concentrations is observed because of potent induction of CYP 3A4, P-gp, UGT1A1 by rifampicin which is likely to result in loss of their therapeutic effectiveness.

Package Leaflet

2. What you need to know before you take rifampicin

Do not take rifampicin

If you are currently taking any of the following medicines:

O Sofosbuvir - antiviral medicine for treatment of hepatitis C virus infections

o Cabotegravir, fostemsavir, lenacapavir – HIV medicines

o Lurasidone

as rifampicin may reduce the blood levels of several medicines including the above listed.

2. ***Paradoxical drug reaction***

If a similar or stricter wording is already included in SmPC and PL, the current wording should remain.

Summary of Product Characteristics

Section 4.4

A warning should be added as follows:

Paradoxical drug reaction

After initial improvement of tuberculosis under therapy with TM, the symptoms may worsen again. In affected patients, clinical or radiological deterioration of existing tuberculous lesions

or the development of new lesions have been detected. Such reactions have been observed within the first few weeks or months of initiation of tuberculosis therapy. Cultures are usually negative, and such reactions do not usually indicate treatment failure.

The cause of this paradoxical reaction is still unclear, but an exaggerated immune reaction is suspected as a possible cause. In case a paradoxical reaction is suspected, symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary. Furthermore, continuation of the planned tuberculosis combination therapy is recommended.

Patients should be advised to seek medical advice immediately if their symptoms worsen. The symptoms that occur are usually specific to the affected tissues. Possible general symptoms include cough, fever, tiredness, breathlessness, headache, loss of appetite, weight loss or weakness (see section 4.8).

Section 4.8

The following adverse reaction should be added under the SOC General disorders and administration site conditions with a frequency common

Paradoxical drug reaction (Recurrence or appearance of new symptoms of tuberculosis, physical and radiological signs in a patient who had previously shown improvement with appropriate anti-tuberculosis treatment is called a paradoxical reaction, which is diagnosed after excluding poor compliance of the patient to treatment, drug resistance, side effects of antitubercular therapy, secondary bacterial/fungal infections.).*

*** Incidence of paradoxical drug reaction: Lower frequency is reported as 9.2% (53/573) (data between October 2007 and March 2010) and higher frequency is reported as 25% (19/76) (data between 2000 and 2010).**

Package Leaflet

2. What you need to know before you take rifampicin

Warning and precautions

Inform your doctor immediately while taking this medicine

● If your symptoms of tuberculosis return or get worse (see 4. Possible side effects)

4. Possible side effects

Common: may affect up to 1 in 10 people

- **Paradoxical drug reaction: Symptoms of tuberculosis can return, or new symptoms can occur after initial improvement during treatment. Paradoxical reactions have been reported as early as 2 weeks and as late as 18 months after beginning anti-tuberculosis treatment. Paradoxical reactions are typically associated with fever, swollen lymph nodes (lymphadenitis), breathlessness, and cough. Patients with paradoxical drug reaction can also experience headaches, loss of appetite, and weight loss.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	05 January 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 February 2026