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 levothyroxine, the scientific conclusions are as follows:

In view of available data on biotin interference with thyroid function tests from spontaneous reports and literature, the majority of the described cases have compatible chronology without confounding factors, laboratory test results returned to normal following withdrawal of biotin or use of a different assay method, indicating a causal association of laboratory interference with biotin. Given the increasingly common use of biotin supplements in high dosage and the prevalence of hypothyroidism with dependence on periodic measurement of thyroid function tests for adjustment of T4 dosage, there is significant potential for clinical mismanagement of these patients based on misleading test results. Determination of biotin intake would be particularly important in situations requiring more exact titration of levothyroxine dosage, such as in pregnant women, in children, in the elderly, and in patients being monitored for residual or recurrent thyroid cancer.

Furthermore, based on the available data on drug-drug interaction between levothyroxine and St. John's Wort from spontaneous reports and literature, including some cases with a suggestive temporal relationship and a positive dechallenge, and given that St. John's Wort is described to be a potent inducer of several liver metabolic enzymes, especially CYP3A, with a similar potency as others known potent enzymatic inducers like rifampicin and phenobarbital which are already listed in the product information (AUC of probe substrates decreased by 80%), this drug-drug interaction with St. John's Wort should be added to the product information of levothyroxine containing products.

Finally, several literature articles which described the interaction between levothyroxine and proton-pump inhibitors (PPIs) were identified by the MAHs. Some cases were identified in their safety databases, with compatible chronology and increased blood TSH or hypothyroidism, which were suggestive of possible lack of efficacy of levothyroxine due to concomitant PPI administration. Studies have shown that gastric acidity enhances the dissolution of levothyroxine tablets. Thus, PPIs, which suppress gastric acid secretion, may decrease absorption of levothyroxine delivered particularly as tablet formulation. The frequency of a concomitant ingestion of levothyroxine and PPI could be considered relatively common given that hypothyroidism and gastric reflux are also common diseases. Like levothyroxine, PPIs are usually taken fasting before breakfast, and their effect lasts 48 hours. Reduced levothyroxine absorption is associated with increased TSH values, generally prompting clinicians to increase the daily dose of levothyroxine tablet, or otherwise to shift the patient to more bioavailable formulations.

The PRAC concluded that the product information of levothyroxine containing products should be amended accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Detailed explanation of the grounds for the differences with the PRAC recommendation

The PRAC recommended to amend the product information of levothyroxine containing products to add the drug-drug interaction between levothyroxine and St John's Wort based on the above-mentioned scientific conclusions.

The CMDh has received a comment from one MS on the wording concerning the drug-drug interaction between levothyroxine and St John's Wort recommended by PRAC for Section 2 of the Package Leaflet, regarding the fact that the indications for St. John's Wort detailed in the proposed wording for the PL (*…an herbal medicinal product <u>used to treat mild depression and mild anxiety</u>*) are not approved indications for St John's Wort in all MSs.

Therefore, CMDh has agreed by consensus that the wording for Section 2 of the Package Leaflet proposed in the PRAC recommendation regarding drug-drug interaction between levothyroxine and St. John's Worth, is amended in order not to detail the example indications of St. John's Worth containing products in brackets. The final amendments proposed to the product information are set out in Annex II.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for levothyroxine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levothyroxine 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 levothyroxine 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:

Interferences with laboratory test:

Biotin may interfere with thyroid immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results. The risk of interference increases with higher doses of biotin.

When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed.

For patients taking biotin-containing products, laboratory personnel should be informed when a thyroid function test is requested. Alternative tests not susceptible to biotin interference should be used, if available. (see section 4.5)

Section 4.5:

Interferences with laboratory test:

Biotin may interfere with thyroid immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see section 4.4).

Package leaflet

Section 2:

Warnings and precautions

[…]

if you are about to undergo laboratory testing for monitoring your thyroid hormone levels, you must inform your doctor and/or the laboratory personnel that you are taking or have recently taken biotin (also known as vitamin H, vitamin B7 or vitamin B8). Biotin may affect results of your laboratory tests. Depending on the test, the results may be falsely high or falsely low due to biotin. Your doctor may ask you to stop taking biotin before performing laboratory tests. You should also be aware that other products that you may take, such as multivitamins or supplements for hair, skin, and nails could also contain biotin. This could affect the results of laboratory tests. Please inform your doctor and/or the laboratory personnel, if you are taking such products (Please note the information in section Other medicines and [Invented name] XX µg).

Other medicines and [Invented name] XX µg […]

If you are taking or have recently taken biotin, you must inform your doctor and/or the laboratory personnel when you are about to undergo laboratory testing for monitoring your thyroid hormone levels. Biotin may affect results of your laboratory tests (see warnings and precautions).

Summary of Product Characteristics

Section 4.5:

Effects of drugs inducing cytochrome P-450: Enzyme-inducing drugs such as … ***products containing St John's Wort (Hypericum perforatum L.)*** *may increase hepatic clearance of levothyroxine, resulting in reduced serum concentrations of thyroid hormone.*

Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these products are given concurrently.

Package leaflet

Section 2:

The effect of <invented name> is influenced by other medications as follows:

[…] products containing St. John's Wort (an herbal medicinal product).

Summary of Product Characteristics

Section 4.5:

Proton pump inhibitors (PPIs):

Co-administration with PPIs may cause a decrease in the absorption of the thyroid hormones, due to the increase of the intragastric pH caused by PPIs.

Regular monitoring of thyroid function and clinical monitoring is recommended during concomitant treatment. It may be necessary to increase the dose of thyroid hormones.

Care should also be taken when treatment with PPI ends.

Package leaflet

Section 2:

Other medicines and [Invented name] XX µg

The effect of [invented name] XX µg is influenced by other medicines as follows:

[…]

Proton pump inhibitors*:*

[…]

Proton pump inhibitors (such as omeprazole, esomeprazole, pantoprazole, rabeprazole, and lanzoprazole) are used to reduce the amount of acid produced by the stomach, which may reduce the absorption of levothyroxine from the intestine and thereby make it less effective. If you are taking levothyroxine while receiving treatment with proton pump inhibitors, your doctor should monitor your thyroid function and may have to adjust the dose of *TM*.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 November 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 January 2023