

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 metformin, the scientific conclusions are as follows:

In view of available data on aggravation of MELAS (Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes) syndrome and MIDD (Maternal inherited diabetes and deafness) in patients taking metformin with known mitochondrial diseases, reported from the literature, spontaneous reports, and in view of a plausible biological mechanism of action, the PRAC considers that a warning on aggravation of MELAS syndrome/MIDD is warranted in patients with known mitochondrial diseases, taking metformin. The PRAC concluded that the product information of products containing metformin 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 metformin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing metformin 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

SmPC section 4.4 Warning and Precaution

Lactic acidosis

At the end of the subsection, addition of:

Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Package Leaflet

Section 2. What you need to know before you <take> <use> X

Warnings and precautions

Risk of lactic acidosis

At the end of the subsection, addition of:

Talk to your doctor promptly for further instructions if:

- **You are known to suffer from a genetically inherited disease affecting mitochondria (the energy-producing components within cells) such as MELAS syndrome (Mitochondrial Encephalopathy, myopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).**
- **You have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 January 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 March 2025