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 metyrapone, the scientific conclusions are as follows:

Based on the cumulative review of haematological adverse reaction reports in the safety database and submitted for review as part of this PSUR, there has been limited information of bone marrow failure events whereas cytopenia events in 3 blood lines have been reported in association with metyrapone use. Therefore, the PRAC recommends to update the section 4.8 of the SmPC to replace the adverse reaction "bone marrow failure" by "leukopenia, anaemia, thrombocytopenia" (frequency remaining not known), which better describes the reported haematological cases.

Based on the review of PSUR data in a context of metyrapone overdose cases, the PRAC considers that an update to SmPC section 4.9 is warranted to amend the outdated information on the general treatment of overdose with gastric lavage and forced emesis, since these measures are not recommended to be used in the current treatment guidelines for routine poisoning management.

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 metyrapone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing metyrapone 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 metyrapone 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 4.8

The following adverse reaction(s) should be updated under the SOC Blood and lymphatic system disorders with a frequency unknown:

leukopenia, anaemia, thrombocytopenia

~~Bone marrow failure~~

Package Leaflet

Section 4

Some side effects may be serious:

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

• ~~Bone marrow failure (occurs in individuals who produce an insufficient~~ **Decrease of** amount of red blood cells, white blood cells or platelets **in blood** and the symptoms may include: bleeding or bruising lasting longer than normal, blood seen in the gums, nose or skin and feeling tired most of the time, shortness of breath, colds that keep coming back~~)~~.

Summary of Product Characteristics

- Section 4.9

The following information should be updated under the subheading Treatment:

Treatment: There is no specific antidote. ~~Gastric lavage (only in case of serious intoxication and if it can be performed shortly after ingestion) and forced emesis should be employed to reduce the absorption of the drug.~~ **Immediate treatment is essential in the management of metyrapone overdose, patients should be referred to hospital urgently for immediate medical attention. Treatment with activated charcoal may be considered if the overdose has been taken within 1 hour.** In addition to general measures, a large dose of hydrocortisone should be administered at once, together with IV saline and glucose. This should be repeated as necessary in accordance with the patient's clinical condition. For a few days blood pressure and fluid electrolyte balance should be monitored.

Package Leaflet

- Section 3

If you take more {Invented Name} than you should

If you take too many capsules, tell your doctor or nurse immediately, or go to your nearest Casualty Department. You may feel sick and have stomach ache and/or diarrhoea. You may also feel dizzy, tired, have a headache, begin sweating and you blood pressure increase. You may need to ~~have your stomach contents emptied~~ **take activated charcoal** and be given hydrocortisone.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 April 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 June 2019