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 amiodarone, the scientific conclusions are as follows:

In view of available data on the literature and spontaneous reports including compatible chronology on the drug-drug interaction between amiodarone and sirolimus leading to increased sirolimus toxicity, the PRAC considers that the weighted cumulative evidence is sufficient to support a causal relationship. The PRAC concluded that the product information of products containing amiodarone should be amended to reflect this drug interaction with sirolimus accordingly.

In view of available data on the literature and spontaneous reports, the PRAC considers a causal relationship between amiodarone and the following adverse reactions: hallucination, neutropenia, agranulocytosis and libido decreased is at least a reasonable possibility. The PRAC concluded that the product information of products containing amiodarone should be amended accordingly.

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 amiodarone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing amiodarone 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 amiodarone 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 4.5

The interaction should be added as follows:

CYP P450 3A4 substrates

- *Other drugs metabolised by cytochrome P450 3A4:* examples of such drugs are lidocaine, **sirolimus,** tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine.

- Section 4.8

The following adverse reaction should be added under the SOC Psychiatric disorders with frequency common:

- **Libido decreased**

The following adverse reaction should be added under the SOC Psychiatric disorders with frequency not known:

- **Hallucination**

The following adverse reaction(s) should be added under the SOC Blood and lymphatic system disorders with frequency not known:

- **Neutropenia**
- **Agranulocytosis**

Package Leaflet

- Section 2 - What you need to know before you take <medicine>

<medicine> may increase the effect of the following medicines:

Ciclosporin**,** ~~and~~ tacrolimus **and sirolimus** – used to help prevent rejection of transplants

- Section 4 – Possible side effects

Common side effects (may affect up to 1 in 10 people)

- **Decrease in sex drive**

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

- **Seeing, hearing or feeling things that are not there (hallucinations)**
- **You may get more infections than usual. This could be caused by a decrease in the number of white blood cells (neutropenia).**
- **Severe reduction in the number of white blood cells which makes infections more likely (agranulocytosis).**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 October 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 December 2021