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 indoramin, the scientific conclusions are as follows:

A causal association has been established between indoramin and QTc prolongation in the context of overdose. Evidence to substantiate this is provided by three clinical studies and 15 supportive cases reported from literature and post-marketing sources. This effect is predominantly observed at higher doses (> 625mg) based on reported doses from 12 of the 15 supportive cases. However, not exclusively so with two cases reporting QTc prolongation at doses of 50mg and 150mg respectively and two studies reporting QTc prolongation at doses of 100mg and 150mg. Four cases reported complications (Torsades de Pointes in three and ventricular fibrillation in one). It is considered that there is sufficient evidence to warrant an update to section 4.9 of the Summary of Product Characteristics, warning of the risk of QTc prolongation in overdose and its management. Corresponding updates is made to section 3 of the Patient information leaflet.

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 indoramin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing indoramin 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 indoramin are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 4.9

Information available at present of the effects of acute overdosage in human beings with indoramin is limited. Effects seen have included deep sedation leading to coma, hypotension and fits.

In cases of overdose QTc prolongation can occur, sometimes complicated by severe arrhythmias, such as Torsades de Pointes.

Results of animal work suggest that hypothermia may also occur.

Suggested therapy is along the following lines:

1. Recent ingestion of large numbers of tablets would require gastric lavage or a dose of ipecacuanha to remove any of the product still in the stomach of the conscious patient.
2. **Cardiac monitoring should be initiated immediately and continued for at least 24 hours.**
3. Ventilation should be monitored and assisted if necessary**.**
4. Circulation support and control of hypotension should be maintained.
5. If convulsions occur diazepam may be tried.

Temperature should be closely monitored. If hypothermia occurs, rewarming should be carried out very slowly to avoid possible convulsions.

Package Leaflet

- Section 3

If you take more Indoramin than you should

If you take more Indoramin than you should, contact your doctor or nearest hospital emergency department immediately. Take the container and any remaining tablets with you. Symptoms of overdose have included deep sedation leading to coma, **irregular heartbeat, changes to your heartbeat (these symptoms can have potentially serious, life-threatening consequences)**, abnormally low blood pressure and fits.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position :	13 July 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 September 2019