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 everolimus (indicated for rejection of transplanted organs), the scientific conclusions are as follows:

The MAH has provided an extensive summary of lymphoedema and mTOR-inhibitors based on literature, preclinical and clinical findings and post-authorisation data. Lymphoedema, and especially lymphocele, are known complications to surgical procedures. Nevertheless, as summarised by the MAH, there are also articles indicating that lymphatic complications could be associated also with medical causes such as mTOR inhibitors-based immunosuppression. A theoretical mechanistic background may involve mTOR inhibitors exerting an impaired healing of lymphatic channels damaged during surgery, as described in two articles.

A cumulative search up to 16 Jan 2019 was performed in Novartis safety database. A total of 102 cases were retrieved cumulatively using these search criteria HLT “Lymphedemas” and PT “Lymphangiogram abnormal”. In no case, a causal association between everolimus and lymphoedema could be definitely established, However, a causal association is inherently difficult to either establish or rule out, given the known risk of lymphatic vessel damage during surgery as a strong confounder

The data, which includes cases in the current PSUR period, presented is not considered to justify labelling of lymphoedema in the SmPC of Votubia but not Certican. Therefore, lymphoedema should be added to Section 4.8 of the SmPC also for Certican, under the SOC Vascular disorders. Regarding the frequency, it is not reasonable to include the same frequency as for Votubia (common), given the uncertainties. Instead a frequency of “not known” is proposed.

The benefit/risk balance for everolimus in the transplantation setting remains positive.

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 everolimus (indicated for rejection of transplanted organs) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing everolimus (indicated for rejection of transplanted organs)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 everolimus (indicated for rejection of transplanted organs)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

lymphoedema, under the System organ class Vascular disorders with a frequency **Not known**.

Package leaflet

Section 4

Other side effects:

Other side effects have occurred in a small number of people, but their exact frequency is unknown:

- **Swelling, feeling of heaviness or tightness, pain, limited mobility of body parts (this could occur anywhere in the body and is a potential sign of an abnormal build-up of fluid in soft tissue due to a blockage in the lymphatic system, also known as lymphoedema)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 May 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 July 2019