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 testosterone (all formulations apart from topical use and testosterone undecanoate injection), the scientific conclusions are as follows:

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Publications based on small size hypothesis-generating studies and published case series reported cases of venous thromboembolism in patients with underlying previously undiagnosed familial or acquired thrombophilia or hypofibrinolysis using testosterone. Thrombosis occurred and reoccurred despite adequate anticoagulation during treatment with testosterone in thrombophilic men and although further evidence may be needed to further substantiate these findings, the hypothesized mechanism of thrombosis in patients with underlying familial thrombophilia that may be mediated by increased E2 levels is not disputed.

Based on the above, it is considered that a warning should be introduced in the product information to exert caution with the use of testosterone in patients with thrombophilia.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing testosterone (all formulations apart from topical use and testosterone undecanoate injection), were warranted.

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 testosterone (all formulations apart from topical use and testosterone undecanoate injection) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing testosterone (all formulations apart from topical use and testosterone undecanoate injection) 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 testosterone (all formulations apart from topical use and testosterone undecanoate injection) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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 4.4

The following warning should be inserted in this section under a heading 'Clotting disorders'. Other warnings related to clotting disorders should also be listed under this heading.

Clotting disorders

Testosterone should be used with caution in patients with thrombophilia, as there have been post-marketing studies and reports of thrombotic events in these patients during testosterone therapy.

Package Leaflet

2. What you need to know before you are given [product name]

Warnings and precautions

Talk to your doctor before using [product name] if you have or have ever had:

[…]

- **blood clotting problems**
    - […]
    - **thrombophilia (an abnormality of blood coagulation that increases the risk of thrombosis - blood clots in blood vessels)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29 October 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 December 2016