Annex I

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

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for testosterone undecanoate (injection), the scientific conclusions are as follows:

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 estradiol 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 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 undecanoate (injection) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing 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 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 products

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

A warning on thrombotic disorders in patients with thrombophilia should be added as follows. In addition, all warnings regarding clotting disorders should be presented under the same subsection 'Clotting disorders'.

Cardiac insufficiency

[…]

~~As a general rule, the limitations of using intramuscular injections in patients with acquired or inherited blood clotting irregularities always have to be observed.~~

Clotting disorders

As a general rule, the limitations of using intramuscular injections in patients with acquired or inherited ~~clotting irregularities~~ **bleeding disorders** always have to be observed.

Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants (see also section 4.5).

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:

[…]

- high blood pressure or if you are treated for high blood pressure, as testosterone may cause a rise in blood pressure.

- blood clotting problems

  - […]

  - **thrombophilia (an abnormality of blood coagulation that increases the risk of thrombosis - blood clots in blood vessels)**

~~high blood pressure or if you are treated for high blood pressure, as testosterone may cause a rise in blood pressure.~~

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