Part VI: Summary of the risk management plan

Summary of risk management plan for testosterone transdermal gel

This is a summary of the risk management plan (RMP) for testosterone transdermal gel. The RMP details important risks of testosterone transdermal gel, how these risks can be minimised, and whether more information will be obtained about testosterone transdermal gel's risks and uncertainties (missing information).

Testosterone transdermal gel's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how testosterone transdermal gel should be used

I. The medicine and what it is used for

Testosterone transdermal gels are approved for testosterone replacement therapy (TRT) in males for the treatment of hypogonadism, when a man has low testosterone levels in their body (see SmPC for the full indication). The product contains testosterone as the active substance, and it is given by applying a gel to your skin (topical gel).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of testosterone transdermal gels, together with measures to minimise such risks and the proposed studies for learning more about these medicinal products, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of testosterone transdermal gel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Cardiovascular events • Thromboembolic risk secondary to haematocrit increase
Missing information	None

II.B Summary of important risks

Important Potential Risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The potential for TRT to cause serious cardiovascular adverse events has been the subject of much debate, not only within clinical medicine, but also with the major regulatory agencies. It is agreed that testosterone and other androgens or anabolic steroids are to be used cautiously in patients with cardiovascular (CV) disorders, renal or hepatic impairment, epilepsy, migraine, diabetes mellitus or other conditions that can be aggravated by oedema, since TRT has the potential to cause fluid retention. Concomitant administration of testosterone and Adrenocorticotropic hormone (ACTH) or corticosteroids may also increase the risk of developing oedema. A study suggested a two-fold increase in the relative risk of myocardial infarctions (MI) in the 90 days after starting TRT in men who had heart disease, compared to the year before. This is supported by some investigators but not by others. In the large matched Canadian cohort study, which included approximately 5 years of follow up, it was concluded that the risk of mortality and CV events was greater with short duration TRT but less with long term TRT. In the 2014 review of Testosterone containing medicinal products done under Article 31 of Directive 2001/83/EC, PRAC concluded that the link between testosterone and CV disease was not proven by available data. PRAC recommended a number of changes to the product information of all testosterone containing medicinal products approved in the European Union. These included; a warning to patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, that testosterone may cause severe complications due to oedema; a precaution for use in men with hypertension; and advice that testosterone levels laboratory parameters such as haemoglobin, haematocrit, liver function tests and lipid profile should be monitored regularly when on long term treatment. Marketing Authorization Holders (MAHs) were also requested to monitor cardiovascular risk (including VTE) and discuss the findings, in the next PBRER. The subsequent 2016 report from PRAC which reviewed these findings, supported the 2014 position. In 2015, US FDA requested a class label warning statement around the risk of heart attack and stroke for testosterone products, based on post-marketing

	reports. There is growing opinion that current evidence is insufficient to confirm an association between TRT and an increased risk of CV adverse events. The Endocrine Society, American Association of Clinical Endocrinologists and two separate reviews by the EU PRAC all agree that such a link has not been proven. It is noted that definitive safety data regarding testosterone therapy must await large, long-term, controlled trials.
Risk factors and risk groups	Elderly men, and men with underlying severe cardiac, hepatic, or renal insufficiency, ischaemic heart disease, hypertension, and other conditions potentially exacerbated by oedema. Use in these groups is covered in the warnings section of the SPC. High doses of testosterone. Patients with high testosterone levels (> 1000 ng/dl).
Risk minimisation measures	Routine risk minimisation measures SPC: Section 4.4 Special warnings and precautions for use Section 4.5 Interactions PIL: Section 2 Warnings and Precautions SPC and PIL: Recommendation to regularly monitor haemoglobin, haematocrit (to detect polycythaemia), liver function, and lipid profile Medicine's legal status: Prescription Only Additional risk minimisation measures: None

Important Potential Risk	Thromboembolic risk secondary to haematocrit increase
Evidence for linking the risk to the medicine	In a meta-analysis study of testosterone RCTs an increase in hematocrit over 50% was the most frequent testosterone-related adverse event in these trials. The number of participants with hematocrit >50% was significantly higher in testosterone-treated men than in placebo-treated men. Testosterone-treated men were 3.67 times more likely to develop hematocrit >50% than were placebo treated men (OR ¼ 3.67; 95% CI, 1.82–7.51) (Calof 2005). Testosterone-induced elevations in hemoglobin (Hb) and hematocrit (Hct) may lead to erythrocytosis, generally defined clinically as Hb > 18.5 g/dl or Hct > 52% in males, though this definition varies. Physiologically, erythrocytosis is defined by an erythrocyte mass that exceeds 125% of that predicted for sex and body mass. This is the most common dose-limiting adverse effect of testosterone therapy. Much of the concern surrounding increases in blood viscosity resulting from increased red blood cell mass centres on the potential increased risk for VTE, myocardial infarction (MI), and cerebrovascular accidents (CVA) (Ohlander 2018). Martinez et al. provides the first evidence for a differential in an adverse effect of testosterone treatment in men with and without pathological hypogonadism, which peaks in the first six months and declines thereafter. The 63% increase in risk in the first six months of testosterone use corresponds to 10.0 (1.9 to 21.6) additional VTEs above the base rate of 15.8 per 10000 person years. Starting testosterone treatment, whether first time or repeat use, is associated with an increased risk of VTE that peaks rapidly in the first three months and declines gradually thereafter. This association is strengthened by a stronger association in the subgroup of patients without a known risk of venous thromboembolism. Overlooking the timing and duration of testosterone use in previous studies could have masked the association between testosterone use and cardiovascular events (Martinez 2016). Two recent studies of 88 patients (67 and 21 altogether) revealed VTE associated with Factor V Leiden (FVL) heterozygosity, the lupus anticoagulant, and lipoprotein(a), peaking three months after starting testosterone therapy (TT). These studies provide further evidence altogether congruent with the 2014 FDA warning on the TT-associated risks of VTE. When TT is given to patients with familial and acquired thrombophilia, thrombosis may occur and recur despite adequate anticoagulation if TT is continued. In patients who have sustained VTE while taking TT, a laboratory evaluation for thrombophilia–hypofibrinolysis should be done. In patients with thrombophilia and a VTE event on TT, the TT should be stopped and not resumed, since recurrent VTE may occur despite adequate concurrent anticoagulation. (Glueck 2018). Walker et al. stated baseline testosterone levels are not associated with increase in VTE risk. However, exogenous testosterone therapy may increase endogenous hematocrit levels, which can increase blood viscosity, platelet accumulation, and thromboxane A2 concentrations for up to 6 months and could subsequently increase risk of blood clot formation and subsequent VTE events. In this case-crossover study comparing 6-month testosterone use for 39,622 men who had a VTE with testosterone use 6 to 12 months before the VTE, use of TT in the 6-month case period was associated with an increased risk of VTE among men with and without hypogonadism. This reconcluded that TT was associated with an increase in short-term risk for VTE among men with and without hypogonadism, with some evidence that the association was more pronounced among younger men. These findings suggest that caution should be used when prescribing TT. (Walker 2020).

Risk factors and risk group:	Excessive increases in haematocrit and correspondingly increased risk for thromboembolism conceivable only with supraphysiological testosterone levels. Patients with additional risk factors for polycythaemia (e.g. chronic obstructive pulmonary disease), venous or arterial thromboembolism may be assumed to be at higher risk. Elderly patients might be at increased risk for the development of increased haematocrit under testosterone treatment (Bhasin 2006, Calof 2005)
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: SmPC sections 4.4, 4.8 Routine risk communication recommending specific clinical measure to address the risk: Recommendations on monitoring haemoglobin and haematocrit (SmPC section 4.4). Other routine risk minimisation measures beyond the Product Information: Androgel is a medicinal product subject to medical prescription, for use as directed by medical practitioner. **Additional risk minimisation measures:** None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of testosterone transdermal gel.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for testosterone transdermal gel.