Part VI: Summary of the risk management plan

Summary of risk management plan for ANDROGEL 16.2 mg/g gel (testosterone)

This is a summary of the risk management plan (RMP) for ANDROGEL 16.2 mg/g. The RMP details important risks of ANDROGEL 16.2 mg/g, how these risks can be minimised, and whether more information will be obtained about ANDROGEL 16.2 mg/g's risks and uncertainties (missing information).

ANDROGEL 16.2 mg/g's summary of product characteristics (SPC) and its package leaflet give essential information to healthcare professionals and patients on how ANDROGEL 16.2 mg/g should be used.

I. The medicine and what it is used for

ANDROGEL 16.2 mg/g and TESTOGEL 1% 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 SPC 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 ANDROGEL 16.2 mg/g, together with measures to minimise such risks and the proposed studies for learning more about ANDROGEL 16.2 mg/g's risks, 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 SPC 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 ANDROGEL 16.2 mg/g. 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	• Transfer events: adverse reactions following secondary exposure to testosterone in women and children • Off label use in athletes
Important potential risks	• Prostate events (prostate cancer, elevated PSA and BPH) • Cardiovascular events • Adverse reactions following use in women and children • Serious adverse events in the elderly
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Transfer events: adverse reactions following secondary exposure to testosterone in women and children	
Evidence for linking the risk to the medicine	Secondary exposure to testosterone in children and women can occur through the use of testosterone gel in men. Regulatory agencies such as the US Food and Drug Administration (FDA) have received post marketing surveillance reports of adverse effects in women and in children ranging in age from nine months to five years who were inadvertently exposed to testosterone through secondary contact exposure with another person being treated with testosterone products, including testosterone gel.
Risk factors and risk groups	Subjects in contact with treated patients
Risk minimisation measures	Routine risk minimisation measures SPC: Section 4.4 Special warnings and precautions for use Section 4.2 Dosage and administration Section 4.6 Fertility pregnancy and lactation PIL: Section 2 Warnings and Precautions Section 2 Pregnancy, breast feeding and fertility

	SPC and PIL: Detailed information on the risk of transfer from skin contact and the steps to take to prevent this. Special advice for pregnant women to avoid risk of contact. Medicine's legal status: Prescription Only Additional risk minimisation measures: None

Important Identified Risk: Off label use in athletes	
Evidence for linking the risk to the medicine	The illegal use of androgens and anabolic steroids by athletes to enhance performance, is well known in body building and some sporting areas. These drugs including testosterone, are often taken at doses well in excess of those used therapeutically and may result in serious health risks. In 2016, The US Food and Drug Administration (FDA) issued a new class wide warning about the abuse potential for all prescription testosterone products, and updated the Abuse and Dependence section of the product information.
Risk factors and risk groups	Athletes, body-builders
Risk minimisation measures	Routine risk minimisation measures: This product is supplied through a doctor's prescription only, so that a proper diagnosis of hypogonadism can be confirmed before the product is made available. SPC: - Section 4.4 Special warnings and precautions for use PIL: - Section 2 Warnings and Precautions - Additional risk minimisation measures: None

Important Potential Risk: Prostate events (prostate cancer, elevated PSA and BPH)	
Evidence for linking the risk to the medicine	The reported prostate events for testosterone gel mainly consist of prostate cancer and benign prostatic hyperplasia (BPH); and it is known that testosterone stimulates production of PSA. Clinical guidelines such as those from Canada strongly advocate against use in prostate cancer and the risks are reflected in the common labelling across products which includes a contraindication for known or suspected prostate cancer and warnings in regard to prostate cancer and BPH. TRT does not appear to significantly worsen lower urinary tract symptoms (LUTS) and is not contraindicated in men diagnosed with BPH, though some guidelines such as those from the Endocrine Society do not support use of testosterone in men with PSA greater than 4 ng/ml. Until relatively recently it was universally accepted that higher serum testosterone caused more rapid growth of prostate cancer and that lower serum testosterone caused less growth and even regression of prostate cancer. This concept arose from the work of Huggins and Hodges in the 1940s; who showed that castration caused both an improvement in clinical symptoms and a decline in serum acid phosphatase in men with metastatic prostate cancer. However, there is no clear evidence to support the hypothesis that men receiving, or with, high testosterone levels have an increased risk of developing prostate cancer. On the contrary, more recent assessment of the evidence in support of

	the relationship between endogenous serum testosterone or other hormones and the risk of developing prostate cancer have led to a conclusion that serum testosterone levels do not play a significant role in the development of the disease. In the British Society for Sexual Medicine UK Policy Statements on Testosterone Deficiency, state that there is evidence indicating that low testosterone levels are associated with aggressive forms of prostate cancer. The 2015 Endocrine Society update to their guidelines for hypogonadism also concludes that there is no new level 1 data to support a definitive connection between testosterone replacement therapy and prostate cancer. It is noted that definitive safety conclusion regarding testosterone therapy must await large, long-term, controlled trials.
Risk factors and risk groups	Existing or previous prostate cancer or BPH. Potential/suggested roles of age, family history, genetics, hormones, race.
Risk minimisation measures	Routine risk minimisation measures SPC: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable Effects Section 5.3 Preclinical safety data PIL: Section 2 Do not use Section 2 Warnings and Precautions Section 4 Possible side effects SPC and PIL: Recommendation for careful examination before and monitoring during therapy (PSA). Medicine's legal status: Prescription Only Additional risk minimisation measures: None

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: Adverse reactions following use in women and children	
Evidence for linking the risk to the medicine	Complications due to off-label use of testosterone products in women and children is reported through the literature and in routine pharmacovigilance. The off-label uses of testosterone in women include low libido, low testosterone levels (hormone replacement therapy), vaginal dryness, or for transgender change.
Risk factors and risk groups	Women and children
Risk minimisation measures	Routine risk minimisation measures: SPC: - Section 4.4 Special warnings and pre-cautions for use - Section 4.6 Fertility pregnancy and lactation PIL: - Section 2 Warnings and Precautions - Section 2 Pregnancy, breast feeding and fertility Medicine's legal status: Prescription Only Additional risk minimisation measures: None

Important Potential Risk: Serious events in the elderly	
Evidence for linking the risk to the medicine	In the past there has been less experience with the use of testosterone in patients over 65 years of age. Together with a significantly higher rate of co-morbidity in this age group, it has led to concern over an increased risk of serious events. In the 2014 EU PRAC review of testosterone containing products, MAH were requested to include a statement in the product information informing that there are limited data regarding elderly patients above the age of 65 years. Companies were also requested to investigate and consider if the pattern of adverse events is comparable to other age groups. With further experience, it is now being proposed by some groups such as the British Society for Sexual Medicine that there is no scientific basis for prohibiting testosterone therapy on the basis of age.
Risk factors and risk groups	Elderly men with significant underlying morbidities, e.g. hypertension, diabetes, obesity, hyperlipidaemia, prostate pathologies. Smoking.

Risk minimisation measures	Routine risk minimisation measures: Due to comorbidities associated with hypogonadism, ANDROGEL 1.62% should be used with caution in the elderly. SPC: - Section 4.2 Dosage and administration - Section 4.4 Special warnings and precautions for use PIL: - Section 2 Warnings and Precautions SPC and PIL: Recommendation for more regular check-ups for the elderly Medicine's legal status: Prescription Only 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 ANDROGEL 16.2 mg/g.

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

There are no studies required for ANDROGEL 16.2 mg/g.