1.6.1 Environmental Risk Assessment – Non-GMO

1.6.1.1 Introduction

This environmental risk assessment was carried out with reference to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00. London, 01 June 2006), that came into effect 1 December 2006.

1.6.1.2 Information on the Product

The applicant has developed a 2 % testosterone gel (TESTAVAN) for the treatment of male hypogonadism.
The TESTAVAN product consists of a pump dispenser and an applicator for dermal self administration of the testosterone gel. The pump contains 85.5 g of gel and is capable of dispensing 56 metered doses of 1.25 mL, each containing 23 mg testosterone. The maximum daily dose is 69 mg testosterone, which will be administered as three metered doses once daily.

The product also contains well-known excipients, Carbomer 980, ethanol, propylene glycol, diethylene glycol monoethyl ether, trolamine, edetate disodium, and purified water, commonly used in pharmaceutical topical products.

1.6.1.3 Risk Assessment Overview

According to the guideline, assessment of potential risks to the environment is a step-wise procedure in which the first phase (phase I) estimates the expected exposure of the environment to the drug substance, while the second phase (phase II tier A and B) is used to perform a risk assessment based on physical/chemical, pharmacological and/or toxicological data.

1.6.1.4 Phase I: Estimation of exposure

1.6.1.4.1 Screening for Persistence, Bioaccumulation and Toxicity

The logKow of testosterone is 3.32 [1]. This value is below the threshold of 4.5 as stated in the guideline and therefore, no further evaluation of persistence, bioaccumulation and toxicity will be needed.

1.6.1.4.2 Calculation of the predicted environmental concentrations

In phase I, the predicted environmental concentrations of the active moiety in the surface water (PEC_{SW}) may be calculated by the formula below. If the PEC_{SW} is below the action limit 0.01 µg/L, and no other environmental concerns are apparent, it may be assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.
This calculation of PEC in surface water assumes

- a percentage of the overall market penetration within the range of existing medicinal products,
- the predicted amount used per year is evenly distributed over the year and throughout the geographic area,
- the sewage system is the main route of entry of the medicinal product into the surface water,

- there is no biodegradation or retention of the medicinal product in the sewage treatment plant, and
- metabolism in the patient is not taken into account.

Calculations of predicted environmental concentration in surface water (PEC_{SW}) of testosterone have been performed as described below.

Calculation of PEC_{SW}

Method of PEC_{SW} calculation given in the guideline

PEC_{SW} [mg/L] = (DOSEai x Fpen)/(WASTEWinhab x DILUTION) DOSEai [mg/inhabitant/day] = Maximum daily dose of active ingredient consumed per inhabitant = 69 mg Fpen [%] = Percentage of market penetration. A default value of 1% (*i.e.* 0.01) is proposed. WASTEWinhab [L/inhabitant/day] = Amount of waste water per inhabitant per day. A default value of 200 is proposed. DILUTION [no unit] = Dilution factor. A default value of 10 is proposed.

Using the default values the following PEC_{SW} is calculated:
PEC_{SW} = (69 x 0.01)/(200x10) = 0.000345 mg/L = 0.345 µg/L

1.6.1.4.2.1 Comparison with action limit

The PEC_{SW} value is above the action limit of 0.01 µg/L, and therefore, the Phase IIA environmental fate and effect assessment of the guideline is triggered.
This comprises the following planned studies:

Study type	**Recommended Protocol**
Adsorption - Desorption Using a Batch Equilibrium Method	OECD 106/ OECD 121/OPPTS 835.1110 (one of these studies)
Ready Biodegradability Test	OECD 301
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	OECD 308
Algae, Growth Inhibition Test	OECD 201
Daphnia sp. Reproduction Test	OECD 211
Fish, Early Life Stage Toxicity Test	OECD 210
Activated Sludge, Respiration Inhibition Test	OECD 209

If in Tier A a potential risk for TESTAVAN to the environment will be identified, then a Tier B assessment should be conducted.

1.6.1.5 Additional information

Regarding the potential endocrine disruptor effects of testosterone, this is a well-known fact. Since the endocrine effect is established in non-clinical studies, according to the Q&A document for the guideline [2] the long-term adverse environmental effects will be characterised in an appropriate fish sexual development test or a fish full life cycle test.

1.6.1.6 Discussion and Conclusion

The PECsw value of the active ingredient of TESTAVAN, testosterone, is above the action limit put forth in the guideline. Therefore a Phase IIA assessment is triggered.
The logKow value of testosterone is below 3.32. Hence, no bioaccumulation will occur.

Concerning the potential endocrine disruptor effects, the Applicant recognizes this potential with TESTAVAN, and this will be evaluated in an appropriate fish study.

1.6.1.7 References

1. Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995., p. 164

2. Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' EMA/CHMP/SWP/44609/2010. 17 March 2011.

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