LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tostrex
(Testosterone)

SE/H/571/01

This module reflects the scientific discussion for the approval of Tostrex. The procedure was finalised at 2006-04-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

ProStrakan Ltd. has applied for a marketing authorisation for Tostrex, 2% (w/w) gel. The active substance is testosterone. The product is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

The proposed clinical dose of testosterone to men is 60 mg (40-80 mg) applied daily to the skin. The serum testosterone levels will be measured 2 hours after application of Tostrex approximately 14 days after initiation of therapy to facilitate titration of the testosterone dose within the physiological range of normal eugonadal men (300-1140 ng/dl).

II. QUALITY ASPECTS

II.1 Introduction

Tostrex 2% gel is presented in the form of gel containing 20 milligrams of testosterone per gram gel. The excipients are propylene glycol, alcohol, isopropyl alcohol, oleic acid, carbomer 1382, trolamine, butylhydroxytoluene and water. The gel is filled in an aluminium canister equipped with a metered dose pump.

II.2 Drug Substance

Testosterone has a monograph in the European Pharmacaopoeia and one of the two manufacturers holds a certificate of suitability of the monograph. Information about testosterone from the other drug substance manufacturer has been supplied in the form of an ASMF.

Testosterone is a white to practically white crystalline powder which is poorly soluble in water. The structure of testosterone has been adequately proven and its physicochemical properties sufficiently described. Relevant information on chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.
Two sources of active substance are used.

II.3 Medicinal Product

Tostrex 2% gel is formulated using excipients described in the current Ph Eur, except for the alcohol that is controlled according to an acceptable in house specification. All raw materials used in the product are of either plant/vegetable or synthetic origin.

The product development has taken into consideration the physicochemical characteristics of the active substance, such as *e.g.* poor aqueous solubility and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies performed and data presented support the shelf life claimed in the SPC, when product is stored at or below 25ºC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This bibliographic application concerns an active compound which is well established. Only local tolerance studies were performed in support of the application and this is considered sufficient.

III.2 Discussion on the non-clinical aspects

The active substance testosterone is well known, and no specific studies with regard to pharmacodynamics, pharmacokinetics and toxicity of the active substance were performed with the exception of new local tolerance studies. Two different formulations among them the formulation intended for clinical use were tested for primary skin irritation in rabbits and dermal sensitisation (modified Buehler patch procedure) in guinea pigs. In conclusion, the local tolerance of Tostrex was satisfactory tolerated in rabbits and in guinea pigs.

Tostrex was considered unlikely to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tostrex gel is intended for testosterone substitution treatment of hypogonadal males.

Being an endogenous substance, testosterone is relatively well known. Therefore, the pharmacokinetic documentation of Tostrex gel 2% mainly consists of bioavailability studies, examining the properties of the gel formulation. This is sufficient.

IV.2 Discussion on the clinical aspects

Clinical pharmacology

Five clinical studies in hypogonadal men were submitted in the national application. In one study the optimal dose and dosing interval of Tostrex was evaluated, to achieve healthy serum testosterone levels of 300-1140 ng/dl. The other studies were designed to compare exposure at different application sites, to study the significance of application area, to study the effects of showering on testosterone levels and to examine the transferability of testosterone from a male to a female through physical contact. The results of the studies are reflected in the SPC.

During the national procedure a question regarding the proposed method for dosing adjustments was raised. After approval in Sweden the sponsor has conducted a study where the validity of the proposed method for dose adjustments was confirmed.

Efficacy and safety
Application of the testosterone gel gave the expected testosterone serum levels along with rises in DHT and estradiol and modest reductions in FSH and LH. This treatment is known to result in improvements in muscular mass, sexual function and even cognitive function. A significant improvement in bone mineral density was confirmed in the present study. There were application site reactions in about half the subjects, which generally resolved without medical intervention. In 10% the subjects withdrew for this reason. However, alternating the application site appears to reduce the rate of application site reactions. From a clinical point of view this mainly bibliographic application appears acceptable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio was considered positive and Tostrex, 2% (w/w) gel has been approved.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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