IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

CosACTHen 0.25 mg/ml solution for injection for dogs

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0461/001/DC
Name, strength and pharmaceutical form	CosACTHen 0.25 mg/ml solution for injection for dogs
Active substances(s)	Tetracosactide
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531 AE Bladel Netherlands
Legal basis of application	Well-established use application (Article 13a of Directive No 2001/82/EC)
Date of completion of procedure	23/10/2019
Target species	Dogs
Indication for use	For the evaluation of adrenocortical function in dogs.
ATCvet code	QH01AA02
Concerned Member States	AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LU, NL, NO, PL, PT, SE, SK, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the reactions that have been observed are indicated in the SPC.
The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The proposed use of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product is a solution for injection and contains 0.25 mg/ ml of tetracosactide as the active substance with the excipients acetic acid glacial, sodium acetate trihydrate, sodium chloride and water for injections. It is packaged in a clear glass vial that is sealed with FluroTec rubber stoppers and an aluminium overseal.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is not described in the European/British Veterinary Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on Intermediate Products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods has been provided. Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

This marketing authorisation application was submitted in accordance with Article 13a (well-established use) of Directive 2001/82/EC, as amended.

CosACTHen 0.25 mg/ml Solution for Injection for Dogs contains the active substance tetracosactide. The product is indicated for the evaluation of adrenal function in dogs. The product is to be administered at a dose of 5 micrograms/kg (0.02 ml/kg) by intravenous or intramuscular injection.

The pharmacodynamic and pharmacokinetic properties of the active substance have been well characterised using published literature. In addition, a proprietary pharmacodynamic study showed that a single intravenous or intramuscular dose of the product at a dose of 5 micrograms of tetracosactide/kg bodyweight resulted in a significantly higher number of positive cortisol responses at 30, 60, 90 and 120 minutes post-dosing when compared to saline controls. In addition, it was demonstrated that adrenal stimulation following administration of tetracosactide via the intravenous and intramuscular routes is equivalent and the post-dose blood sample should be taken between 60 and 90 minutes after administration of the product, to adequately capture peak cortisol response.

The pharmacokinetics of tetracosactide (described as ACTH-immunoreactivity (IR) since immunoassays cannot distinguish the active substance from endogenous ACTH) have been described through reference to studies in the public domain. Peak levels of IR-ACTH are attained rapidly (T_{max}, 30 minutes) whilst return to baseline levels is also rapid (120 minutes; data for 5 microgram/kg dose level). Peak IR-ACTH levels are greater for the intravenous route of administration when compared to the intramuscular route, despite similar cortisol responses.

Toxicological Studies

No single- or repeat-dose toxicity studies have been provided; however, reference was made to a target animal safety study in which CosACTHen was administered to dogs once per week for three weeks, via the IV or the IM route, at doses of up to 280 or 112 µg/kg, respectively. No adverse toxicological findings were reported. No studies have been provided in support of reproductive or development toxicity. However, extensive literature examining the effects of the downstream cortisol increases have been provided that indicate a small risk to the developing foetus; therefore, appropriate warnings have been included in the SPC.

The absence of genotoxicity and carcinogenicity studies has been adequately justified.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

Estimated exposure for accidental self-injection has been compared with a NOAEL from the TAS study giving an acceptable margin of exposure. Such an approach was accepted given that the TAS study was accepted as being a representative model of an acute accidental self-injection that may be experienced by a user, so is considered acceptable for use as a TRV in the URA. Dermal absorption is considered unlikely based on the molecular size of the peptide (active substance).

Irritation and sensitisation tests have been performed using the final formulation and in accordance with appropriate OECD guidelines. Findings from these studies indicate that the product is not a skin or eye irritant and does not have skin-sensitising potential. However, literature indicates that skin sensitisation can occur and is severe in individuals with allergic disorders; therefore, appropriate warnings have been included in the SPC.

Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product.

Environmental Risk Assessment

An environmental risk assessment was provided. It was accepted that the assessment can end at Phase I and that the product will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the SPC.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

Results of a proprietary target animal safety study were provided along with a number of literature references in which the safety of tetracosactide has been investigated. Based on the findings from this study and the studies cited in the published literature, the SPC includes appropriate information on the potential adverse reactions that may occur following administration of the product. Vomiting was observed commonly during clinical studies and application site bruising (IM route of administration), injection site haematoma (IV route of administration), depression, diarrhoea, lameness, and nervousness occurred uncommonly during clinical studies.

As no data supporting safety of use during pregnancy and lactation were provided, the product should not be used in pregnant or lactating animals. ***IV.B Clinical Studies***

The results of one proprietary field study and numerous literature references which evaluated very similar formulations to the proposed formulation were provided in support of field efficacy of the product. These data provides sufficient evidence to conclude that the proposed use of tetracosactide, namely, evaluation of adrenocortical function in dogs, is well-established. A number of published literature references were cited where studies have indirectly considered the effects of other medicinal products on the results of ACTH stimulation testing in healthy dogs. Based on the information provided, it was concluded that before performing an ACTH stimulation test, it should be ensured that a sufficient wash-out period has elapsed since the administration of any medicinal product which may either cross-react with the cortisol assay, or have an effect on the hypothalamic-pituitary-adrenal (HPA) axis.

Based on the data provided, it was accepted that the indication for this product has been adequately supported.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.
This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Changes:

None.