ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Alizin 30 mg/ml Solution for Injection

PuAR correct as of 24/07/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0187/001/E/002
Name, strength and pharmaceutical form	Alizin 30 mg/ml Solution for Injection
Applicant	Virbac S.A. 1ère avenue – 2065 m - L.I.D. – 06516 Carros, Cedex France
Active substance(s)	Aglepristone
ATC Vetcode	QG03XB90
Target species	Dogs (bitches)
Indication for use	Induction of abortion up to 45 days after mating.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition Procedure in accordance with Article 13 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	18 May 2011
Date product first authorised in the Reference Member State (MRP only)	23 October 2001
Concerned Member States for original procedure	Austria Belgium Bulgaria Czech Republic Denmark Estonia Finland Germany Greece Hungary Iceland Ireland Italy Latvia Lithuania Luxembourg The Netherlands Norway Poland Portugal Romania Slovakia Slovenia Spain Sweden

I. SCIENTIFIC OVERVIEW

Alizin 30 mg/ml Solution for Injection is authorised for use in dogs (bitches) for induction of abortion up to forty five days after mating. The product contains aglepristone 30 mg/ml as an active substance. The product should be administered subcutaneously at dosage rate of 10 mg per kg of bodyweight of aglepristone, twice, 24 hours apart.

Alizin 30 mg/ml Solution for Injection was submitted as a full application and granted a National MA in the UK in October 2001. The product had already been marketed as Alizine in France since 1996. The product went through the Mutual Recognition Procedure in November 2003 followed by a first wave repeat use procedure in 2005. This application is for a second wave repeat use procedure.

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 slight reactions observed are indicated in the SPC[1]. The product is safe for the user (refer to the SPC, there is a potential serious risk for pregnant women), and for the environment when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy 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. Composition

The product contains the active substance aglepristone and excipients anhydrous ethanol and refined arachis oil.

The product is presented in vials in volumes of 5, 10 and 30 millilitres, with bromobutyl stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the current guidelines.

The choice of formulation is justified.

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 from a licensed manufacturing site.

[1] SPC - Summary of Product Characteristics

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance, aglepristone, has no monograph in the European Pharmacopoeia (Ph. Eur). The manufacturer provided details of a testing monograph, and this was considered acceptable. The active substance is manufactured in accordance with the principles of good manufacturing practice.

All excipients are described in the Ph. Eur. Compliance with the requirements of the pharmacopoeia is therefore applied as the specification for each of these ingredients. This is considered acceptable.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products.

F. 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 have been provided.

G. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life. The shelf-life of the veterinary medicinal product as packaged for sale is 3 years. An in-use shelf life of 28 days is justified.

H. Genetically Modified Organisms

Not applicable

J. Other Information

A shelf life of 3 years and in-use shelf life of 28 days is justified, subject to the following storage warnings:

- Keep the vial in the outer carton in order to protect from light.
- Should any apparent growth or discoloration occur, the product should be discarded

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided data which indicate that in vitro, aglepristone shows strong antiprogestrone activity, similar to one of its parent compounds mifepristone. It also shows strong affinity for mineralocorticoid and oestrogen receptors. In vivo, antiprogestrone activity is greater by the oral route than subcutaneous route in rats and rabbits, and has no effect topically in the rabbit. The limited pharmacokinetic data available indicate that aglepristone is absorbed relatively slowly and eliminated very slowly after subcutaneous administration in the target species.

Toxicological Studies

Single dose toxicity:
GLP compliant acute dose studies using the oral and subcutaneous routes of administration was conducted in mice and rats. Additionally, an acute subcutaneous and intramuscular tolerance study in the rabbit was also provided. The active, aglepristone, appeared to be of low oral toxicity in mice and rats when given by the oral route in aqueous suspension. Clinical signs were generally minor in nature and were more apparent on the day after dosing. These resolved within a few days after dosing.

Mutagenicity
The applicant conducted three *in vitro* and one *in vivo* GLP[2]-complaint mutagenicity studies using aglepristone. The active substance, aglepristone, did not show any mutagenic potential in these studies.

Other Studies

A GLP complaint maximisation test for skin sensitisation was conducted on guinea pigs which indicated that the active ingredient was not sensitising.

[2] Good Laboratory Practice

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline addressing the potential exposure routes to the operator. The use of Alizin 30 mg/ml Solution for Injection is not expected to present an undue hazard to the user. The product literature and SPC contain the following safety warnings:

- Nor-steroids are used in humans to induce abortion.
- Accidental injection may be a particular hazard to women who are pregnant, intending to become pregnant or whose pregnancy status is unknown.
- Care should be taken by the veterinary surgeon when handling the product and the person restraining the dog to avoid accidental injection.
- Pregnant women should administer the product with caution.
- This is an oil-based product that may cause prolonged local reactions at the site of injection.
- In case of accidental injection, seek urgent medical advice and show the doctor this warning.
- Women of child-bearing age should avoid contact with the veterinary medicinal product or wear disposable plastic gloves when administering the veterinary medicinal product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guidelines which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Pharmacology

Pharmacodynamic:
Aglepristone is a synthetic steroid counteracting the effect of progesterone by competing with this hormone at the level of the uterine receptors, resulting in abortion (or resorption) within 7 days after administration.

Aglepristone does not modify progesterone, prostaglandins, oxytocin or cortisol plasma concentration within 24 hours after its administration but it induces a discharge of prolactin within 12 hours.

In vitro, the affinity of aglepristone for the progesterone receptors in the uterus of the dog is 3 times higher than that of progesterone.

The relative binding affinity of aglepristone to glucocorticoid receptors is similar to that of dexamethasone but aglepristone has antagonistic properties.

Pharmacokinetics
After 2 injections of 10 mg/kg/day at a 24-hour interval, the maximal concentration (approximately 280 ng/ml) is reached after 2.5 days. The mean residence time is around 6 days, this period includes the mean absorption time from the injection site.

After administration of a 10 mg/kg radio-labelled dose, the excretion of radioactivity is very slow. Only 60 % of the administered dose is excreted during the first 10 days and around 80 % over 24 days.

Excretion is essentially via the faeces (around 90 %).

Tolerance in the Target Species of Animals

The applicant provided a review of published literature and in addition provided reports on studies conducted with aglepristone. The pivotal tolerance study demonstrated that general tolerance to aglepristone was excellent. The local reactions were erythema, oedema, skin thickening and inguinal lymph node enlargement. These reactions were dose dependent and decreased spontaneously within a few weeks. The injection of aglepristone produced signs of pain in some bitches, but this was not of a lasting nature. The pain reaction only consisted of whining and there was no licking or scratching at the injection site. Similar local reactions were observed in the dose effect/pharmacokinetic study. Tolerance in the field was also studied in two extensive trials. These studies concluded that the use of aglepristone did not increase the incidence of uterine infections.

IV.B Clinical Studies

The applicant provided a review of published literature and in addition provided reports on original studies. These studies indicated that aglepristone, when administered according to the dosage regime, is efficacious in a very high percentage of bitches.

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.

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)