I. INTRODUCTION

This product is a solution for injection containing 250 µg/ml cloprostenol. It is indicated for intramuscular administration to cattle for the treatment of suboestrus or non-detected oestrus, induction of birth, termination of normal or abnormal pregnancy, chronic endometritis, ovarian luteal cysts and for controlled breeding. The dose rate in this species is single or repeated 2 ml doses. In horses, the product is indicated for the induction of luteolysis following early foetal death and resorption, termination of persistent dioestrus and of pseudopregnancy, treatment of lactation anoestrus, establishing oestrous cycles in barren or maiden mares and as an aid in stud management. The dose rate in ponies is 0.5-1.0 ml and in larger horses is 1-2 ml.

This application is submitted under Article 13 (1) of the Directive 2001/82/EC as amended by Directive 2004/28/EC. The applicant has confirmed that the formulation of Juramate Solution for Injections is identical to the formulation of an approved product and the manufacturing procedures used to formulate both products are the same, therefore no bioequivalence or bioavailability data have been presented.

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 product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

Product Development and Composition

The product contains the active substance cloprostenol and the excipients chlorocresol, sodium chloride, sodium citrate, citric acid anhydrous, sodium hydroxide and water for injection.

The product is packaged in a cardboard box containing one clear glass (type I) vial of 20 ml, closed with a chlorobutyl rubber stopper and aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and presence of preservative have been justified.

The product is an established pharmaceutical form and its development has been adequately described in accordance with the relevant European guidelines.

Active Substance

The active substance is cloprostenol and is described in the British Pharmacopoeia (Veterinary) (BP (Vet)). Supplementary tests and limits for named impurities and residual solvents have also been provided.

Other Substances

All the excipients used in the formulation are supplied against Ph. Eur. monographs and are commonly used in veterinary medicines. Apart from the chlorocresol preservative, the sodium chloride, sodium citrate and citric acid form the buffer system and the sodium hydroxide is used, if necessary, to modify the pH to the correct range. This is acceptable. The level of the preservative is justified as it is at the same level as the pioneer product.

Packaging Materials

The container is a 24 ml clear, colourless type I, glass bottle containing 20 ml of the solution. The containers are closed with chlorobutyl rubber stoppers and a crimped aluminium seal is put over this. Both the glass bottle and rubber stoppers are declared to comply with the relevant sections of the Ph. Eur. The secondary pack is a printed cardboard box containing one vial and a package leaflet

Manufacture of the Finished Product

The applicant has provided a flow chart and description of the manufacturing process. The manufacturing process involves a mixing and dissolution process. Appropriate checks are carried out during the manufacture and filling processes. The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

The applicant has declared that no materials used in the manufacture of this product fall into the scope of the TSE guideline and has provided a declaration and format 3 table and these are satisfactory.

Finished Product Quality Control

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 were provided.
Batch analytical data from the proposed production site were provided demonstrating compliance with the specification.

Stability of the Product

Active substance

The stability data were provided in an active substance master file which contains confidential information about the active substance. These data indicate that the molecule is stable and was assigned a retest period of 24 months.

Finished Product

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

A shelf life of 3 years and in-use shelf-life of 28 days was considered justified under the appropriate storage conditions: Protect from light.

A variation to increase the shelf life from two years to three years was approved in March 2011.

CONCLUSIONS ON QUALITY

The product is appropriately formulated and controlled. A shelf-life of three years in unopened container was justified. An in-use shelf life of 28 days was also justified.

III. SAFETY ASPECTS

Pharmacology

Since the application was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity, data on pharmacodynamics and pharmacokinetics were not required. This type of product is exempt from the requirements to provide bioequivalence studies.

Toxicology

Since the application was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity, data on toxicology were not required. This type of product is exempt from the requirements to provide bioequivalence studies.

User Safety

The following operator warnings are included in the SPC and product literature:

- Prostaglandins of the $F_{2\alpha}$ type can be absorbed through the skin and may cause bronchospasm or miscarriage.
- Care should be taken when handling the product to AVOID SELF-INJECTION OR SKIN CONTACT.
- Women of child-bearing age, asthmatics and persons with bronchial or other respiratory problems should avoid contact with the product, and should wear disposable plastic gloves when administering the product.
- The possible incidence of bronchospasm with the product is unknown. Should shortness of breath result from accidental inhalation of injection, seek urgent medical advice and show the doctor this warning.
- Accidental spillage on the skin should be washed off immediately with soap and water.

The operator warnings are identical to those included in the SPC and product literature for the comparator product.

Residues

Since the application was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information was not required.

The following withdrawal periods were justified:

Cattle should not be slaughtered for human consumption within 24 hours after administering the product.
It is not necessary to discard milk from treated cattle.
Do not administer to horses intended for human consumption

Environmental Safety

Since the application was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information was not required. Appropriate disposal advice is included on the SPC and product literature.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety
The user warnings are identical to those included in the SPC and product literature for the comparator product and are acceptable.

Conclusions on Consumer Safety
The meat withdrawal period of 24 hours and the warnings on the SPC are identical to the comparator product and are considered satisfactory to protect consumer safety

Conclusions on Environmental Safety
This information was not required and appropriate disposal advice is included on the SPC and product literature

IV. EFFICACY

Clinical Pharmacology
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information is not required as it has already been presented for the reference product.

Tolerance in the Target Species
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity new tolerance data is not required as it has already been presented for the reference product.

Resistance
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity resistance data is not required as it has already been presented for the reference product.

Clinical Efficacy
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity this information is not required as it has already been presented for the reference product.

CONCLUSIONS ON EFFICACY
The pharmaceutical formulations of the reference and test product are identical with regard to the nominal content of the active ingredients. No new pharmacological, target species tolerance or clinical field studies were presented because of the nature of the application. The same efficacy claims and warnings were therefore justified for Juramate Soltuion for Injection.

PART V. OVERALL CONCLUSION ON THE PRODUCT

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

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)