I. INTRODUCTION

Equimidine was formally known as Equisedan, the name was changed during a post authorisation variation on the 29th March 2006. Equimidine is a solution of detomidine hydrochloride for injection. It is used to sedate horses requiring procedures such as clinical examination or minor surgery. Detomidine hydrochloride acts by inhibiting transmission in the central nervous system, reducing consciousness and raising the pain threshold. Following its administration, sedation may be deepened by injection of butorphanol. Short-term anaesthesia may be induced by successive injection of Equimidine and ketamine.

Dosage is dependent upon the effect required, from 0.1 ml per 100 kg of the animal's bodyweight for slower induction of light sedation to 0.8 ml per 100 kg for rapid, profound sedation.

The application for a Marketing Authorisation for Equimidine was made on the basis of its essential similarity* to the established product, Domosedan (Vm 03469/4000), first authorised in February 1985 and marketed in the UK by Pfizer Ltd. For this type of application, applicants are exempted from the usual requirement to produce evidence of safety and efficacy, if they show that the composition of the proposed product is essentially similar to, i.e. closely resembles, that of an established product, i.e. one authorised in the EU for more than 10 years.

II. QUALITY ASPECTS

Product Development and Composition

The product is a sterile, aqueous solution, appropriately presented in clear glass, multi-dose vials sealed with a pierceable rubber stopper, allowing removal of the appropriate dose volume. In addition to detomidine hydrochloride at 10 mg per ml, the solution contains methyl hydroxybenzoate at 1 mg per ml as preservative, shown effective in controlling microbial contamination that might be introduced during removal of doses. Sufficient sodium chloride is added to render it isotonic with blood. Dilute sodium hydroxide is used to adjust to the same pH (degree of acidity) as that of the pioneer product, Domosedan. Each vial nominally contains 10 ml of solution, sufficient for 3 to 5 average treatments.

In justifying essential similarity, the applicant has pointed to the comparability of the composition of Equimidine with that of Domosedan. Both products are simple aqueous solutions, administered intravenously so that the active ingredient is immediately available. Ingredients of an appropriate quality are employed in the preparation of the product. The active ingredient is obtained in high purity and negligible degradation of Detomidine occurs in long-term storage of Equimidine.

Active Substance

The dossier includes details of the manufacture and control of the active ingredient, presented by its manufacturer. The monograph of the European Pharmacopoeia for detomidine hydrochloride has been taken as the basis for the specification. Additional testing is applied to ensure that potential impurities arising from the specified method of synthesis are limited in accordance with current guidelines and that the material is in other respects suitable for use in an injectable product. The methods of analysis have been shown to be valid and data obtained on several batches show that the specification is consistently met.

* This means that the application was made under the provisions of Article 13.1.a.iii of Directive 2001/82/EC.

Other Ingredients
These comply with the tests specified in the relevant monograph of the British or European Pharmacopoeia, including any additional requirements for materials used in injectable products.

Packaging Materials
Glass vials and rubber closures that form the container for the product comply with the relevant pharmacopoeial monographs for components used on injectable products.

Manufacture of the Product
All production steps are performed according to GMP[1]. The solution is manufactured and filled in a suitable environment using recognised production techniques. Data show that a clean, sterile product of the expected potency is consistently produced.

Finished Product Quality Control
The specification for the finished product controls appropriate parameters, including appearance, content of active ingredient and preservative, volume of contents, pH and sterility. Data show the suitability of the analytical methods employed in testing.

Batch analysis data have been supplied on 3 batches of the product, showing that consistently satisfactory results are achieved.

Stability

Active Substance
The manufacturer of the active substance has presented data on its stability, assessing material stored under long-term and accelerated test conditions against requirements of the pharmacopoeial monograph. Batches of pilot-scale and full-scale manufacture are under test in packaging representative of commercial containers. Data so far available indicate that the substance is very stable. On present evidence, testing for compliance with the specification should be conducted annually. Tests are continuing with the expectation that this re-test interval will be extended.[2]

Finished Product
The dossier contains stability data on three batches of the product subjected to accelerated testing and to long-term testing under standard test conditions. The results of 12 months testing are available. Negligible changes have been observed when the product is examined against the requirements of the proposed end-of-life specification, supplemented with relevant additional tests, such as those for preservative efficacy. Long-term testing is continuing. The data originally justified a shelf-life of 24 months for the product, this has now been extended to 3 years. No special restriction on the temperature of storage is required, but the product should be protected from light by storing the vial in the outer carton.

In-Use
In-use stability testing has been carried out on vials of the product subjected to storage under accelerated temperature conditions. To simulate normal usage, doses were removed at intervals throughout the test period and the product has been shown to remain in compliance with relevant requirements of the specification for 28 days.

[1] GMP – Good Manufacturing Practise.
[2] A variation procedure authorised in December 2011 extended this period to 5 years.

CONCLUSIONS ON QUALITY

The supporting data demonstrate that the injection solution is suitably formulated and quality-controlled. Data show that Equimidine is essentially similar to the established product, Domosedan. A shelf-life of 3 years is justified, without restriction on the temperature of storage, subject to the following storage warnings:

Store the product in the outer carton in order to protect from light. Protect from light. Store in a dry place. Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

III. SAFETY AND RESIDUES ASPECTS

The application was based on essential similarity of Equimidine to the established product Domosedan. The product is a solution intended solely for intravenous administration and contains the same active substance as Domosedan, another intravenous solution already approved for use in horses. This provides proof of essential similarity, and the applicant therefore did not need to submit additional data to demonstrate this. Since essential similarity has been shown, there is no requirement to present further data to demonstrate the safety of the product for man or the environment.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The product has the same user warnings as Domosedan because the risk to the user is the same. The agreed warnings are as follows:

- In the case of accidental oral intake or self-injection, seek medical advice immediately and show the package leaflet to the doctor but DO NOT DRIVE as sedation and changes in blood pressure may occur.
- Avoid skin, eye or mucosal contact.
- Immediately after exposure wash the exposed skin with large amounts of fresh water.
- Remove contaminated clothes that are in direct contact with the skin.
- In the case of accidental contact of the product with eyes, rinse with large amounts of fresh water. If symptoms occur, seek the advice of a doctor.
- If pregnant women handle the product, special caution should be observed not to self-inject as uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.

Conclusions on Consumer Safety

The following withdrawal periods are listed on the SPC and product literature:
Meat and offal: 2 days
Milk: 12 hours

Conclusions on Environmental Safety

This application was made on the basis of essential similarity to an established product, and is exempt from the requirement for ecotoxicity testing because environmental safety aspects of the established product have already been considered.

IV. CLINICAL ASPECTS

This application for a Marketing Authorisation was based on essential similarity to the established product Domosedan. The product is a solution intended solely for intravenous administration and contains the same active substance as Domosedan, another intravenous solution already approved for use in horses. This provides adequate proof of essential similarity and the applicant therefore did not need to provide additional data to demonstrate this.

Since essential similarity has been demonstrated, there is no requirement to present new pharmacological, tolerance or clinical efficacy data.

CONCLUSIONS ON CLINICAL ASPECTS

The pharmaceutical formulations of the reference and test product are essentially similar and the safety warnings and claims made are the same as those for the established product. Safety and efficacy in horses are therefore considered satisfactory.

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 man 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)