IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Intra-Epicaine 20 mg/ml solution for injection for horses

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Intra-Epicaine 2.0% w/v Solution for Injection
Active substance(s)	Mepivacaine hydrochloride
Applicant	Dechra Regulatory B.V., Handelsweg 25, 5531 AE Bladel, Netherlands
Legal basis of application	Bibliographical application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of Authorisation	1st December 2006
Target species	Horses
Indication for use	For infiltration, nerve block, intra-articular and epidural anaesthesia in horses.
ATCvet code	QN01BB03

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 slight reactions 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 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.Qualitative and Quantitative Particulars

The product contains the active substance mepivacaine hydrochloride (2% w/v) and the excipients sodium chloride, sodium hydroxide and water for injections.
The container/closure system consists of clear glass vials with red chlorobutyl rubber stoppers and aluminium seals.
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.

C.Control of Starting Materials

The active substance is mepivacaine hydrochloride, an established substance described in the European 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

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

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

A.1 Precise Identification of the Product concerned by the Application

Mepivacaine (N-(2-6-dimethylphenyl)-1-methyl-2-piperidine-carboxamide; synonym: chlorocain, carbocaine) is a racemic tertiary amide local anaesthetic used as its hydrochloride salt in horses. The concentration available for horses is a 2 % solution.

A.2 Pharmacological Studies

A.2.1 Pharmacodynamics:

The mechanism of action of mepivacaine is to prevent the generation and conduction of the nerve impulse. Conduction is blocked by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that is produced by a slight depolarisation. This action is due to a direct effect with voltage-sensitive Na+ channels.
Mepivacaine exists in both charged and uncharged forms at physiological pH while the intracellular environment favours formation of the active, charged molecule. The

onset of action of mepivacaine is, therefore, rapid (2-4 minutes) with an intermediate duration of action (about 1 hour).

A.2.2 Pharmacokinetics

Peak venous levels of mepivacaine have been measured in mares following caudal epidural anaesthesia or caudal subarachnoid anaesthesia. The maximum venous concentrations were similar (0.05 µg/ml) and were reached in 51-55 minutes. In a separate study, mepivacaine or its metabolites appeared in the urine within 15 minutes of subcutaneous injection and reached peak levels within 2-6 hours. It was largely cleared from the urine within 24 hours. The major metabolite in horse urine is 3-hydroxymepivacaine.

A.3 Toxicological Studies

The applicant has provided bibliographical data to demonstrate the toxicological profile of the product.

The intravenous LD_{50} values in mice and rats were 35 to 44 mg/kg bw and 35 mg/kg bw for dl-mepivacaine, 34 to 49 mg/kg bw and 37 mg/kg bw for l-mepivacaine, and 32 to 40 mg/kg bw and 36 mg/kg bw for d-mepivacaine, respectively. In mice after subcutaneous administration, there were differences in the LD_{50} values for the mepivacaine isomers, the d-isomer being the more toxic (175 mg/kg bw) than the dl-mepivacaine (280 mg/kg bw) and the l-mepivacaine (330 mg/kg bw). In rats, however, these differences were not significant (LD_{50} values of 500 to 530 mg/kg bw). In repeat dose studies in mice, cumulative toxic effects of mepivacaine are largely absent: there was no apparent accumulative toxicity of rapid repeat dosing (8 doses every 30 min) of half the LD_{50} dose of mepivacaine. Case reports in man indicate that cumulative toxic effects can be seen, but these are rare.

The general toxicity associated with mepivacaine is similar to that seen with other amide local anaesthetics. Toxicity of amides is manifest in the cardiovascular system and the CNS with the CNS up to five times more sensitive. Thus, adverse reaction is initially manifest by CNS stimulation (e.g. twitching and seizure) followed by depression (drowsiness, unconsciousness and death secondary to respiratory arrest). Effects on the cardiovascular system are generally secondary to CNS effects and are due mainly to myocardial depression.

No reproductive toxicity, including embryotoxicity/foetotoxicity studies were presented. Mepivacaine crosses the placenta. There is, however, no evidence that this compound is associated with reproductive toxicity or teratogenic effects.

Mutagenicity data are limited, but mepivacaine showed no genotoxicity in mouse micronuclear tests. No carcinogenicity studies were provided, but this is considered acceptable given the widespread use of the active substance and the absence of reports of carcinogenicity.

A.4 Studies of other effects

The data provided by the Applicant indicate that local anaesthetics, including mepivacaine, can cause allergic reactions in man but this is very rare. The effects and side effects of mepivacaine and lidocaine during epidural anaesthesia were

compared: the onset and duration of anaesthesia were similar in both groups. Mild hypotension was more prolonged in the mepivacaine group.
The interaction of mepivacaine and other local anaesthetics with phagocytes has been determined in vitro: mepivacaine at 1 mg/ml inhibit neutrophil production of superoxide anion and hydrogen peroxide and neutrophil adhesion or phagocytosis. Theoretically, this action could impact on inflammation and healing.
Studies in the rabbit indicate that mepivacaine causes intradermal irritation, slight eye irritation and intramuscular irritation at the injection site.

A.5 User Safety

Mepivacaine is used as a local anaesthetic, including epidural anaesthesia, in man. The dose in man is up to 7 mg/kg bw. Systemic toxic effects are usually only seen following erroneous injection (e.g. intravenous injection), although mild systemic toxicity has been reported under normal conditions of use.
The principle routes of exposure are dermal, ocular or inadvertent self-injection.
It is accepted that the proposed user safety statements are appropriate and, if observed, use of this product is unlikely to pose a significant hazard to the user.

A.6 Environmental Risk Assessment

Given the proposed indications for use of this product it is accepted that it will be used in a small number of individual animals only, for infrequent treatments. Consequently, use of the product is unlikely to pose a risk to the environment.

III.B Residues Documentation

Not applicable. The product is not to be used in horses intended for human consumption. Treated horses may never be slaughtered for human consumption. The horse must have been declared as not intended for human consumption under national horse passport legislation.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

A.1 Pharmacology
See above.

A.2 Tolerance in the Target Species of Animals
No tolerance studies in the horse have been provided. However, no signs of systemic intolerance to mepivacaine under normal conditions of use have been described in the published literature and, based on pharmacovigilance experience in the UK (where the product has been authorised since 1990) where few cases of adverse effects have been reported, it can be concluded that the product is well tolerated. The pharmacovigilance experience from the UK is supported by two expert

statements. Both consider mepivacaine an effective local anaesthetic agent for perineural and intra-articular nerve block and both advise that the principal adverse effects encountered relate to local swelling, but that the incidence of local swelling is rare.

A.3 Resistance
Not applicable.

IV.B Clinical Studies
The Applicant has provided bibliography, in the form of review articles describing nerve blocking techniques as well as specific clinical studies of conditions causing lameness, that supports the use of mepivacaine for infiltration, peripheral nerve block and epidural and intra-articular anaesthesia in the horse. The bibliography is further supported by a clinical expert statement: the equine orthopaedic expert, based on extensive experience with Intra-Epicaine, describes mepivacaine as a potent, rapidly acting, efficacious and safe local anaesthetic solution for use in the horse.
The indications and proposed posology are supported by the data presented.

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.

Quality Changes

Summary of change **(Application number)**	**Approval date**
Change in the name and/or address of the marketing authorisation holder	dd/mmmm/yyyy
