ADVICE SUMMARY
APPLICATION FOR REGISTRATION OF A CHEMICAL PRODUCT

Product name: CEFOMAX POWDER FOR INJECTION
Applicant: JUROX PTY LIMITED
Product number: 64773
Application number: 49238

Purpose of Application and Description of Use: Registration of a 50 mg/ml ceftiofur sterile aqueous injection product for the treatment of respiratory tract infections in horses and cattle, and urinary tract infections in dogs.

Active Constituent: Ceftiofur sodium

Regulatory Decision:
To grant the application subject to the following conditions:

Standard Conditions of Registration/Approval


Non-Standard Conditions of Registration/Approval
The label affixed to containers must:
(a) comply with the requirements of the Vet Labelling Code as relevant to the product and published in the APVMA Manual of Requirements and Guidelines (MORAG), or otherwise, any prescribed APVMA Labelling Standard, whichever is in effect at the time;
(b) not contain any information inconsistent with the relevant particulars for label approval as defined by section 3 of the Agvet Code that have been determined by the APVMA.

The label affixed to containers must comply with any statutory conditions of label approval that are at any time prescribed by the Agvet Code Regulations 1995 for the purposes of paragraph 23A(1)(a) of the Agvet Code.
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External Efficacy Reviewer

Cefomax Powder for Injection claims to be a safe treatment of respiratory infections in horses and cattle, and urinary tract infections in dogs. The APVMA deemed the product to be similar to Excenel Powder for Injection Injectable Antibiotic, the reference product (APVMA 45748). Jurox Pty Limited addressed the efficacy and safety aspects of the product with scientific arguments and literature, which an External Reviewer assessed.

The Reviewer considered the properties of the active constituent, the functions of the non-active constituents and the nature of the product. The Reviewer accepted arguments that the particle size and amorphous characteristics of the powder would not present a barrier to dissolution and cited Craigmill (1997) who observed total bioavailability of ceftiofur sodium following five consecutive intramuscular doses of either 1.1 or 2.2 mg ceftiofur free acid equivalents/kg to a non-target species. Slovis and co-workers (1997) observed similar concentrations of ceftiofur and its metabolite, desfuroylceftiofur, in plasma following intravenous and intramuscular administration of a dose of 2.2 mg/kg to horses.

References supported the effectiveness of ceftiofur when administered as a parenteral solution at the label recommended dose rate of 1 mg/kg bw intramuscularly in cattle, 2 mg/kg bw intramuscularly in horse and subcutaneously in dogs. Urine concentrations of ceftiofur remained above the MICs for Escherichia coli and Proteus mirabilis for over 24 hours in dogs (Brown et al 2008). Plasma ceftiofur (1.279 µg/mL) from horses was well above the MIC90 for Streptococci (≤ 0.03 µg/mL) and Pasteurella (≤ 0.015 µg/mL) for 24 hours and Escherichia coli (≤ 0.5 µg/mL) for 12 hours (Slovis et al 2006). At the recommended dose and route for cattle, MacNeil (1996) cited a Cmax of 4.12 ± 0.84 µg/mL obtained in calves. This peak concentration of ceftiofur was substantially higher than the MIC90 of ≤ 0.03 µg/mL for European isolates of Pasteurella multocida, Mannheimia spp and Haemophilus somnus.

Jurox Pty Limited correctly argued that the non-active constituents of the product would not affect the safety of Cefomax Powder for Injection. Despite the pH of the reconstituted test product being different to the reference, the Reviewer concluded that the likelihood of pH differences altering absorption or bioavailability of ceftiofur was remote. This conclusion was based on the rapid and complete absorption of ceftiofur and its extensive metabolism to desfuroyloceftiofur when the sodium and hydrochloride salts of ceftiofur are administered. In addition, differences in pH have implications for stability and pain at the injection site. As the reference product causes pain at the injection site, the test product is expected to have a similar effect.

Cattle appeared to tolerate up to 20 times the recommended dose with only slight irritation at the injection site. At the label recommended dose in horses, Mahrt (1992) recorded no decrease in food consumption and none of the horses showed an increase in muscle irritation with increasing dose. Overall, Kausche and Robb (2003) and other authors provided evidence that ceftiofur is well tolerated at the recommended dose rate, irrespective of the parenteral route of administration.
### Data relied on to provide the advice

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<td>EXCENEL RTU (50 mg/mL Suspension for Injection for Pigs and Cattle. Summary of Product Characteristics (SPC) Renewal V1</td>
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<td>EXCENEL 4G Sterile Powder for Solution for Injection. Summary of Product Characteristics (SPC)</td>
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<tr>
<td>42496</td>
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<td>Mahrt, C.R.</td>
<td>Safety of ceftiofur sodium administered intramuscularly in horses (Abstract)</td>
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<td>42493</td>
<td>S</td>
<td>Kausche, F.M. and Robb, E.J.</td>
<td>A Comprehensive Review of Ceftiofur Sodium and Hydrochloride Formulations for Treatment of Acute Bovine Foot Rot.</td>
<td>2003</td>
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<td>42495</td>
<td>S</td>
<td>MacNeil, J.D.</td>
<td>Residues of some veterinary drugs in animals and foods: Ceftiofur.</td>
<td>1996</td>
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<td>42476</td>
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<td>Pharmaceutical equivalence of Cefomax Powder for Injection and the reference product</td>
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* S = Data submitted with the application