ADVICE SUMMARY

APPLICATION FOR REGISTRATION OF A CHEMICAL PRODUCT

Product name: QUADRANT DRY COW INTRAMAMMARY ANTIBIOTIC
Applicant: VIRBAC (AUSTRALIA) PTY LTD
Product number: 65805
Application number: 52066

Purpose of Application and Description of Use: Registration of a cephalonium dihydrate (250 g cephalonium/syringe) intramammary antibiotic product for control of mastitis-causing bacteria (including penicillin-resistant strains) in non-lactating dairy cattle.

Active Constituent: Cephalonium dihydrate

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

Standard Conditions of Registration/Approval


ADVICE
APVMA Veterinary Residues Team

Virbac Australia Pty Ltd proposed a 21-day withholding period for meat and a 49-day treatment calving interval for the use of Quadrant Dry Cow Intramammary Antibiotic in non-lactating dairy cows while observing existing MRLs (0.02 mg/kg for milk, and 0.1 mg/kg in meat and edible offal) and residue definition for cephalonium (parent cephalonium). The product is not intended for lactating cows. The Veterinary Residues team assessed data from one tissue and one milk residues trial submitted to support these proposals.

In the tissue residue trial cephalonium residues in kidneys were below LOD at all other sampling times from day 21 onwards, while residues in liver, muscle and fat were below LOD at all sampling times. These results support that cephalonium residues in tissues are likely to comply with existing Australian MRLs. On this basis, the Veterinary Residues team assigned a WHP for meat of 21 days.

In the milk residue trial cephalonium residues peaked at the fifth milking post-calving. Statistical analysis of the milk residues data showed that cephalonium residues in milk are likely to comply with the existing MRL for milk within 84 hours after calving. Based on these results, the Veterinary Residues team supported a 49-day treatment to calving interval and assigned a WHP for milk of 96 hours (8 milkings).

The Veterinary Residues team also conducted a dietary exposure assessment and reported the chronic dietary exposure to cephalonium residues in relation to the toxicological and microbiological ADIs is acceptable. An acute dietary exposure assessment was not conducted, as an ARfD for cephalonium has not been established.

Virbac Australia Pty Ltd proposed an ESI of 21 days, same as the domestic WHP. In determining an ESI for Quadrant Dry Cow Intramammary Antibiotic, the Veterinary Residues Team considered that there are no Codex CXLs for cephalonium and the CIS, EU, Korea, Taiwan and the USA have not established MRLs/tolerances for the antibiotic. As Japanese provisional MRLs of 0.01 mg/kg for cephalonium in bovine tissues are lower than the method LOQ (0.025 mg/kg) for cattle meat and offal, the method LOD (0.005 mg/kg) for cephalonium was taken as the endpoint for ESI determination for cattle meat and offal. Results from the tissue residues trial indicate that cephalonium residues in muscle, liver, kidney and fat were below the method LOD 21 days after treatment and will be non-detectable. Therefore, an ESI of 21 days was supported.

Australian cheese, butter/butter fat and milk powders are exported rather than raw milk. The Veterinary Residues Team concluded that the original method LOQ (0.02 mg/kg) for cephalonium residues in bovine milk was still an acceptable concentration for trade considerations of cephalonium residues in milk processed for dairy exports. This conclusion was based on: (i) the original LOQ being lower than the MIC50 and MIC90 values reported in scientific literature for cephalonium; (ii) residues levels at or lower than the method LOQ do not inhibit the actions of starter cultures used to produce cheeses and yoghurt; (iii) cephalonium not considered to be lipophilic and does not preferentially partition into milk fat; (iv) statistical analysis of the milk residues data showing that cephalonium residues in milk are likely to be less than the method LOQ when the 49-day treatment to calving interval and 96 hours (8 milkings) milk WHP are observed.
External Efficacy Reviewer

Quadrant Dry Cow Intramammary Antibiotic is an intramammary preparation that contains 89.9g/kg cephalonium dihydrate, but no dye. Each single dose syringe of the product provides 250 mg cephalonium. The product is indicated to provide control and protection against bacteria that cause mastitis in non-lactating dairy cows. An External Reviewer assessed four publications and two comparative studies that included the pioneer reference product, Coopers Dry Cow Intramammary Antibiotic (APVMA 47940).

Published references by Gruet et al (2001) and Kirk et al (1994) provided an overview of the problems associated with mastitis. These authors highlighted the importance of preventing and controlling mastitis through the use of intramammary antibiotics coupled with best on-farm husbandry and management practices. Shephard et al (2004) provided support for the use of cephalonium dihydrate as a dry cow therapy in Australia.

An in vitro study conducted by the applicant (2007) using a paper disc agar plate method, tested the susceptibility of various bacterial isolates (n=20) to three concentrations of cloxacillin, and cephalonium provided by the test and reference products. The test product inhibited 16 of 20 isolates and showed no significant difference in activity when compared to the reference product (p>0.05). Enterobacter faecium, Pseudomonas aeruginosa, Enterobacter aerogenes and Corynebacterium ulcerans were resistant to cephalonium and cloxacillin.
In a comparative field study, quarters of Friesian cows allocated to two study groups (Curative and Preventative) were aseptically prepared and treated with one tube (250 mg cephalonium) of either the test or reference product. Within 6-28 hours post-calving, milk samples were collected on three occasions and were examined bacteriologically. The unit of analysis was a single quarter. Results from the trial indicated that both cure and preventative rates were not dissimilar for both intramammary products.

From this comparative study, thirty field isolates of \textit{S. aureus}, including 10 coagulase negative isolates, were examined for their sensitivity to cephalonium, 3 aminoglycosides and 2 penicillins using a disc diffusion method. There were no isolates resistant to cephalonium.

The Reviewer concluded that the trial results support that Quadrant Dry Cow Intramammary Antibiotic could achieve comparable efficacy results as the reference product with regards to the control of sub-clinical mastitis in dairy cows during the drying-off period.

### Data relied on to provide the advice

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<td>Virbac Australia Pty Limited</td>
<td>A comparative controlled study of two cephalonium based intramammary formulations for the treatment and prevention of sub clinical mastitis in non-lactating dairy cows under New Zealand conditions</td>
<td>2007</td>
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<td>25291</td>
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<td>Antibiotic Susceptibility Testing by Paper-Disc Agar Plate Method</td>
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<td>25296</td>
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<td>P Gruet, P Maincent, X Berthelot, V Kaltsatos</td>
<td>Bovine mastitis and intrammary drug delivery: review and perspectives</td>
<td>2001</td>
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<td>JH Kirk F Degraves J Tyler</td>
<td>Recent progress in treatment and control of mastitis in cattle</td>
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<td>RW Shepherd S Burman P Marcun</td>
<td>A competitive field trial of Cephalonium and cloxacin for dry cow therapy for mastitis in Australian dairy cows</td>
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* *S = Data submitted with the application*