

# NOTICE

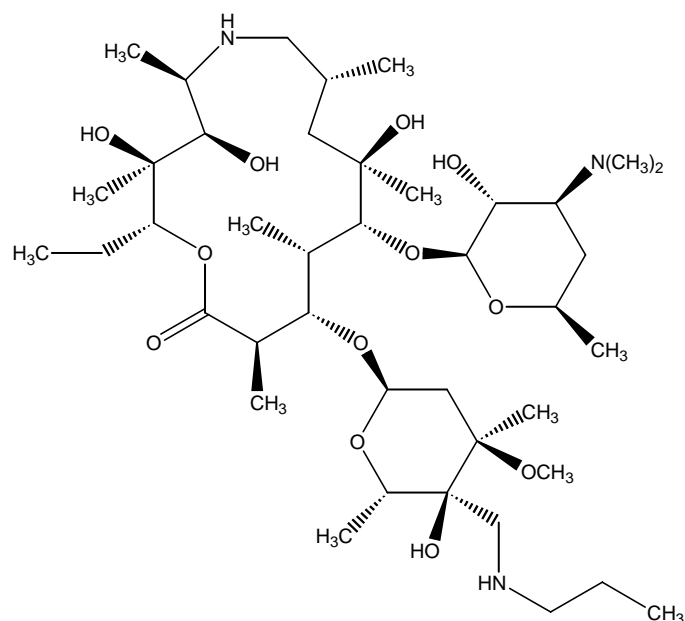
## Tulathromycin

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application for the approval of a new active constituent, tulathromycin. Tulathromycin is a new semi-synthetic macrolide prepared by fermentation followed by organic synthesis which is proposed for use as a treatment of bacterial respiratory disease in cattle and pigs. It is a member of triamilide subclass of macrolide antibiotics. The technical tulathromycin active constituent consists of a ca. 99:1 ratio of two isomers which in the formulated product equilibrate to a ca. 9:1 ratio. The active constituent tulathromycin is optically active.

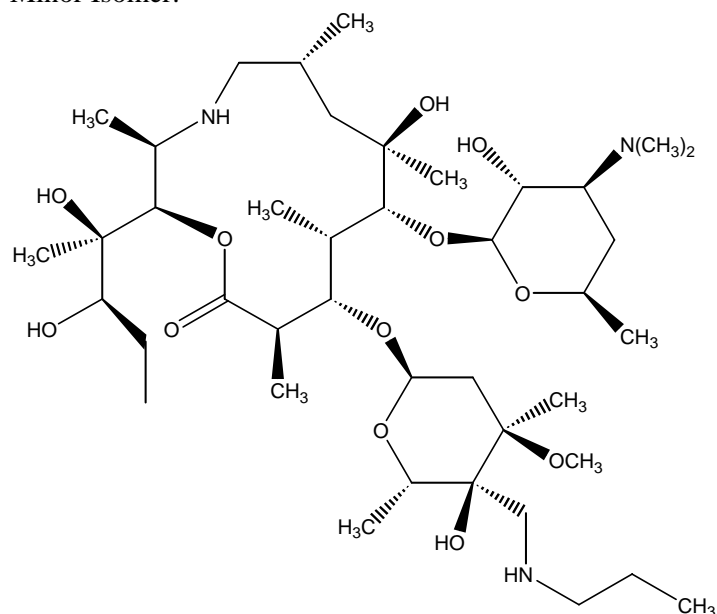
In accordance with section 12 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for approval of tulathromycin should be granted. Submissions should state the grounds on which they are based. Such grounds should relate only to the matters that the APVMA is required to take into account in deciding whether to grant the approval. Comments must be received by the APVMA within 28 days of the date of this Gazette.

### Particulars of the Active Constituent

Common Name:	Tulathromycin
CA Names:	Major Isomer: (2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,8 <i>R</i> ,10 <i>R</i> ,11 <i>R</i> ,12 <i>S</i> ,13 <i>S</i> ,14 <i>R</i> )-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C[(propylamino)methyl- $\alpha$ -L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one and Minor Isomer: (2 <i>R</i> ,3 <i>R</i> ,6 <i>R</i> ,8 <i>R</i> ,9 <i>R</i> ,10 <i>S</i> ,11 <i>S</i> ,12 <i>R</i> )-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C[(propylamino)methyl- $\alpha$ -L-ribo-hexopyranosyl]oxy]-2-[(1 <i>R</i> ,2 <i>R</i> )-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclopentadecan-13-one
CAS Number:	217500-96-4 (major isomer) and 280755-12-6 (minor isomer)
Manufacturer's Codes:	CP-472,295 (major isomer), CP-547,272 (minor isomer), CP-472,295(e) (equilibrated mixture), triamilide (mixture)
Minimum Purity:	94.0% w/w
Molecular Formula:	C <sub>41</sub> H <sub>79</sub> N <sub>3</sub> O <sub>12</sub>
Molecular Weight:	806.23
Structure:	Major Isomer:



and  
Minor Isomer:



Chemical Family:

Triamilide subclass of macrolide antibiotics

Mode of Action:

Inhibition of essential protein biosynthesis by selective binding to bacterial 50S ribosomal subunits

### **Summary of the APVMA's Evaluation of Tulathromycin Active Constituent**

The Chemistry and Residues Program of the APVMA has evaluated the chemistry aspects of tulathromycin active constituent (manufacturing process, quality control procedures, batch analysis results, stability and analytical methods) and found them to be acceptable.

On the basis of the data provided, it is proposed that the following APVMA Active Constituent Standard be established for tulathromycin active constituent:

Constituent	Specification	Level
Tulathromycin	Tulathromycin	Not less than 940 g/kg (anhydrous,

Other compounds of toxicological significance are not expected to occur in tulathromycin as a result of the raw materials and the synthetic route used.

The Office of Chemical Safety of the Therapeutic Goods Administration has considered the toxicological aspects of tulathromycin, and advised that there are no toxicological objections to the approval of this chemical.

A microbiological acceptable daily intake (ADI) of 0.005 mg/kg bw/d is recommended based on a MIC<sub>50</sub> of 1 µg/mL in the most sensitive bacterial genus, *Bifidobacterium spp*, found in the human GI tract. The microbial ADI is supported by a toxicological ADI established at 0.005 mg/kg bw/d derived from a 12-month dog study and increased liver enzymes at the next highest dose and a 1000-fold safety factor. An Acute Reference Dose (ARfD) of 0.1 mg/kg bw, based on a lowest-observed-effect-level (LOEL) of 100 mg/kg bw in a dog oral acute study, using a safety factor of 1000, have been established.

The National Drugs and Poisons Schedule Committee (NDPSC) has included tulathromycin into Schedule 4 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

The APVMA accepts the findings and recommendations of its advisers on these criteria.

The APVMA is satisfied that the proposed importation and use of tulathromycin would not be an undue toxicological hazard to the safety of people exposed to it during its handling and use.

Written submissions on the APVMA's proposal to grant approval for tulathromycin should be addressed in writing to:

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