MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

KEYTIL 300 mg/ml + 90 mg/ml solution for injection
TILDOKET 300 mg/ml + 90 mg/ml solution for injection

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0280/001/DC
Name, strength and pharmaceutical form	KEYTIL 300 mg/ml + 90 mg/ml solution for injection (AT, BE, CZ, DE, ES, IE, IT, NL, PL, SK) TILDOKET 300 mg/ml + 90 mg/ml solution for injection (LT, LV, RO, PL)
Applicant	VETPHARMA ANIMAL HEALTH, S.L. Les Corts, 23 08028 - Barcelona Spain
Active substance(s)	Tilmicosin Ketoprofen
ATC Vet code	QJ01RV01
Target species	Cattle (calves ≤ 330 kg)
Indication for use	For therapeutic treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica* susceptible to tilmicosin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13b "Fixed combination" of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	Day 210: 23/10/2018
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	AT, BE, CZ, DE, IE, IT, LT, LV, NL, PL, PT, RO, SK

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, the consumer of foodstuffs from treated animals 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains tilmicosin (300 mg/ml) and ketoprofen (90 mg/ml) as active substances and benzyl alcohol as preservative. BHT and propyl gallate are included as antioxidants. Other excipients are phosphoric acid, propylene glycol and water for injections.

The container/closure system consists on polypropylene vials of 50 ml, 100 ml and 250 ml, closed with bromobutyl rubber stopper and sealed with an aluminium capsule. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

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 from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance tilmicosin is described in the USP and ketoprofen is described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substances specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications have been provided.

For tilmicosin, the information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Scientific data and certificate of suitability issued by the EDQM have been provided for ketoprofen.

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 have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance tilmicosin have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. For ketoprofen, a retest period is included in the certificate of suitability issued by the EDQM.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (2 years), when stored under the approved conditions.

Appropriate data have been provided to support the in-use shelf-life of the product.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that:

Tilmicosin is an antimicrobial agent belonging to the macrolide antibiotics group. The antibacterial action is based on the inhibition of protein synthesis by reversibly binding to 50S subunits of the ribosome. It has bacteriostatic action but at high concentrations it may be bactericidal. Tilmicosin is active against the following microorganisms which are involved in respiratory diseases in cattle: *Pasteurella multocida* and *Mannheimia haemolytica*.

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). Ketoprofen has anti-inflammatory, analgesic and antipyretic properties. Effects are obtained partially by the inhibition of prostaglandin and leukotriene synthesis by ketoprofen, acting on cyclooxygenase and lipoxygenase respectively. Ketoprofen inhibits thrombocyte aggregation.

The applicant has also provided bibliographical data which show that following a single subcutaneous dose of tilmicosin, it has a good tissue penetration and accumulation, with consistently higher concentration in lungs than in serum. The available metabolic studies did not indicate extensive metabolism of the parent compound. Besides the parent compound, in excreta and liver of cattle two major (T1 and T2) and one minor metabolite (T3; not in liver) were present. In faeces and urine of cattle, approximately 20 and 65% of the total residue respectively, was parent tilmicosin. Elimination of tilmicosin from blood serum is relatively slow. Approximately 70% of the administered dose is excreted via faeces and approximately 20% via urine.

Toxicological Studies

The applicant has provided bibliographical data which show that

- Single Dose Toxicity
  Tilmicosin is potentially toxic to the cardiovascular system. The heart is the target of toxicity in animals. Data on acute oral LD_{50} in cattle was 150 mg/kg, and 97 mg/kg after subcutaneous administration in mice.

  Ketoprofen has LD_{50} of approximately 500 mg/kg bw in mice, rabbits and dogs. In rats, the results were from 30 to 480 mg/kg bw. Clinical signs reported were those usually observed with other NSAIDs.

- Repeated Dose Toxicity
  The lowest NOEL was 4 mg/kg/day for tilmicosin (dogs, oral, 12 months).
  For ketoprofen, a NOEL could be established in three one month-studies (rats in feed: 6 mg/kg/day; rats oral: 2 mg/kg/day; dogs oral: 2 mg/kg/day) and in one 6-month oral study in baboons (4.5 mg/kg bw/day).

- Reproductive Toxicity, including Teratogenicity:
  For tilmicosin, in teratogenicity studies with rats and rabbits, tilmicosin was not teratogenic or embryotoxic. The NOAEL for maternotoxicity was 10 mg/kg bw/day.

  Regarding ketoprofen, it was maternotoxic in rats at 9 mg/kg bw/day and the toxicological NOEL for teratogenicity was established at 2 mg/kg bw (rabbits, oral). In fertility studies in rats, effects of Ketoprofen on male and female reproduction functions were observed at doses higher than 3 mg/kg/day.

- Mutagenicity

  Tilmicosin has not mutagenic effects in the mutagenicity tests (both *in vitro* bacterial and *in vitro* and *in vivo* mammalian).
  Ketoprofen and its main metabolite are not mutagenic, based on the set of mutagenic tests performed.

- Carcinogenicity:
  The absence of carcinogenicity potential has been demonstrated for both substances.

Other Studies

The applicant has provided bibliographical data which show that

Tilmicosin presents immunomodulatory properties, mainly simultaneously suppressing the activation of T- and B-cells in mice *in vitro* and *in vivo*.

Ketoprofen has significantly suppressive effects on humoral immunity. Regarding neurotoxicity, concentrations of 0.1% and 1% given intrathecally resulted in a statistically significant increase in the number of neurons presenting alterations, particularly in the cervical and thoracic spinal cord.

The components of the VMP can produce skin and eye irritation, as well as sensitization reactions.

Observations in Humans

The applicant has provided bibliographical data which show that

as other NSAIDs, the main adverse effects observed in humans are associated with the gastrointestinal system.

Tilmicosin is not used in human therapy due to its cardiotoxic potential which can be fatal when injected. Accidental injection can cause nausea, numbness of lips and tongue, vomiting, and headache, among other symptoms. Skin exposure results in redness and tingling of the skin, and eye exposures in stinging and swelling.

Microbiological Studies

The applicant has provided bibliographical information which shows that

tilmicosin has a NOAEL of 400 mg/kg bw in an in vivo study with human gut flora associated (HFA) germ-free rats. In animals, the NOAEL was established at 0.4 mg/kg/day.

Ketoprofen and its residues do not have microbiological properties.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main route of exposure is the accidental self-injection.
Due to tilmicosin can cause fatalities in human beings following injection of high doses of substances, SPC section 4.5.ii contains a frame with yellow background colour with stringent user safety warnings.
Moreover, the product can produce an eye and skin irritation, as well as it can cause allergic reactions too. Also there is a risk for pregnant women that must be taken into account.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the PEC_{soil} value for all categories of target species is below the trigger value.

III.B Residues documentation

Residue Studies

A residue depletion study using the final formulation has been conducted in cattle. Samples of liver, kidney, fat and injection site (core and surrounding) were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period. Statistical analysis of the results was used to set the withdrawal period.

The analytical method was an HPLC-MS/MS for the determination of tilmicosin and ketoprofen. The method was fully validated.

MRLs

Tilmicosin and ketoprofen are included in table 1 of the Annex to Commission Regulation No. 37/2010 as pharmacological actives substances with the following MRLs:

Active substance	Marker residue	Animal species	MRL	Target tissues
Tilmicosin	Tilmicosin	All other food producing species except poultry	50 µg/kg 50 µg/kg 1 000 µg/kg 1 000 µg/kg 50 µg/kg	Muscle Fat Liver Kidney Milk
Ketoprofen	Not applicable	Bovine Porcine *Equidae*	No MRL required	Not applicable

The excipients benzyl alcohol and propylene glycol are included in Table 1 of Regulation 37/2010 and no MRL is required. Propyl gallate, butylhydroxytoluen and phosphoric acid are authorized as food additives. Food additives are included in Table 1 of Regulation 37/2010 and no MRL is required.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 93 days for cattle meat and offal is justified. The withdrawal time established is considered adequate to grant the consumers safety.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

One MIC study was carried out by the applicant to determine the status of resistant strains.

The applicant also conducted two well-designed Pharmacokinetic studies using the two drugs in combination.

Tolerance in the Target Species of Animals

One tolerance study was carried out and the results obtained are well documented in the SPC.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory Trials

The applicant conducted a study that assessed 3 doses of Ketoprofen and selected the targeted one. This dose was later used in the field assay.
For confirmation purposes, a PK/PD for tilmicosin was conducted. The applicant used data obtained in Pharmacokinetic studies performed and in the MIC study.

Field Trials

A field trial in 3 sites was conducted to evaluate the efficacy and safety of the VMP for the treatment of naturally occurring Bovine Respiratory Disease (BRD). Performed in accordance with Good Clinical Practices guidelines, this was a blinded, randomized, positive-controlled study. The results obtained documented the safety and efficacy of the VMP.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 veterinary Heads of Agencies website (www.hma.eu).

This section 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.

None