ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, ANIMAL SPECIES AND MARKETING AUTHORISATION HOLDERS IN THE CONCERNED MEMBER STATES

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharmaceu-tical form	Animal species	Frequency	Recommended dose Route of administration
Austria	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim Germany	Micotil - Injektions-lösung für Rinder	300 mg/ml	Solution for injection	Cattle (calves and heifers)	Single dose	10 mg of tilmicosin/kg bw subcutaneous use
Belgium	Eli Lilly Benelux Stoofstraat 52 1000 Brussels Belgium	Micotil	300 mg/ml	Solution for injection	Cattle, sheep	Single dose	10 mg/kg bw subcutaneous use
Czech Republic	Eli Lilly Regional Operations GmbH Elanco Animal Health Barichgasse 40-42 A-1030 Wien Austria	Micotil 300 inj. ad us. vet.	300 mg/ml	Solution for injection	Young cattle (bovine) Not for use in cows producing milk for human consumption	Single dose	1 ml for 30 kg bw (i.e. 10 mg of tilmicosin/kg bw) subcutaneous use
France	Lilly France 13 rue Pages 92158 Suresnes cedex Paris France	Micotil 300	300 mg/ml	Solution for injection	Bovine	Single dose	10 mg/kg bw subcutaneous use
Germany	Lilly Deutschland GmbH Abt. ELANCO Animal Health Teichweg 3 D-35396 Gießen Germany	Micotil 300	300 mg/ml	Solution for injection	Cattle (not to be used in lactating cows)	Single dose	10 mg tilmicosin per kg bw, corresponding to 1 ml Micotil 300 per 30 kg bw subcutaneous use
Greece	ELANCO ELLAS Messogion 335 Av, 15231 Athens Greece	Micotil 300	300 mg/ml	Solution for injection	Cattle, sheep	Single dose	10 mg tilmicosin/kg bw subcutaneous use
Hungary	Eli Lilly Regional Operations GmbH Barichgasse 40-42 A-1030 Wien Austria	Micotil 300 Injection A.U.V.	300 mg/ml	Solution for injection	Cattle (calf)	Single dose	10 mg tilmicosin/kg bw subcutaneous use

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharmaceu-tical form	Animal species	Frequency	Recommended dose Route of administration
Ireland	Eli Lilly & Company Ltd. Elanco Animal Health Kingsclere Road Basingstoke Hampshire RG21 6XA United Kingdom	Micotil Injection	300 mg/ml	Solution for injection	Cattle and sheep	Single dose	All sheep indications and pneumonia in cattle: 1ml Micotil per 30 kg bw (equivalent to 10mg tilmicosin per kg bw). Interdigital necrobacillosis in cattle: 0.5 – 1ml Micotil per 30 kg bw (equivalent to 5-10mg tilmicosin per kg bw) subcutaneous use
Italy	Eli Lilly Italia S.p.A Elanco Animal Health Via Gramsci, 733 Sesto Fiorentino, 50019 Firenze Italy	Micotil 300	300 mg/ml	Solution for injection	Cattle, sheep and rabbit	Single dose	10 mg tilmicosin/kg bw (1 ml/30 kg bw) subcutaneous use
Netherlands	Eli Lilly Nederland B.V. Postbus 379 3990 GD Houten The Netherlands	Micotil 300	300 mg/ml	Solution for injection	Cattle and calves up to 2 years of age; Non-lactating sheep	Single dose	10 mg tilmicosin/kg bw subcutaneous use
Poland	Eli Lilly (Suisse) S.A. ul. Stawki no. 2, 21 pietro 00-193 Warsaw Poland	Micotil 300	300 mg/ml	Solution for injection	Bovine	Single dose	1 ml/30 kg bw subcutaneous use
Portugal	Lilly Farma – Produtos Farmacêuticos, Lda Rua Dr. António Loureiro Borges, 4 – piso 3 Arquiparque – Miraflores 1495-131 Algés Portugal	Micotil	300 mg/ml	Solution for injection	Calves	Single dose	10 mg tilmicosin per kg bw (1ml per 30 kg bw) subcutaneous use
Slovak Republic	Eli Lilly Regional Operations Oblina 54 90027 Bernolakova, Slovak Republic	Micotil	300 mg/ml	Solution for injection	Young cattle	Single dose	10 mg Tilmicosinum/ kg bw equivalent to 1 ml per 30 kg bw, during 3-4 days subcutaneous use.
Slovenia	Iris mednarodna trgovina d.o.o Cesta v Gorice 8, SI-1000 Ljubljana, Slovenija	Micotil 300	300 mg/ml	Solution for injection	Cattle	Single dose	1 ml Micotil 300 per 30 kg bw (10 mg tilmicosin/kg bw) subcutaneous use

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharmaceu-tical form	Animal species	Frequency	Recommended dose Route of administration
Spain	Lilly S.A. Elanco Valquimica S.A. Avda. de la Industria, 30 28108 Alcobendas Madrid Spain	Micotil 300	300 mg/ml	Solution for injection	Cattle	Single dose	10 mg tilmicosin/kg bw subcutaneous use
United Kingdom	Eli Lilly Industries Ltd Elanco Animal Health Kingsclere Road Basingtstoke Hampshire RG21 6XA United Kingdom	Micotil	300 mg/ml	Solution for injection	Cattle Sheep (over 15kg)	Single dose	Sheep: 10 mg/kg bw Cattle: Pneumonia: 10 mg/kg bw Interdigital necrobacillosis: 5 mg/kg bw subcutaneous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MICOTIL (see Annex I)

Introduction

Tilmicosin is a macrolide antibiotic synthesized from tylosin which has an antibacterial spectrum similar to tylosin with enhanced activity against *Pasteurella multocida* and *Pasteurella haemolytica*.

Tilmicosin can cause fatalities in human beings following injection of high doses of the substance.

Concerns were raised concerning the adequacy of the existing safety warnings and conditions for use of the product in protecting users from self-injection and its potential serious consequences as well as the need to provide adequate information for medical action in case of such an occurrence or abuse of the product (suicide).

Two fatalities following accidental injection of Micotil were reported in the United States but no accidental human fatality has ever been reported in Europe since the introduction of Micotil. However, serious adverse reactions after accidental injection have been reported. Some of these cases required hospitalisation.

Overall risk assessment

The risk : benefit analysis for Micotil is rather complex and various risk management proposals must be carefully considered.

Benefits

Micotil is a single-injection, low volume treatment and therefore has benefits of ease of use, animal welfare and compliance with dosage regimen. The fact that the product is administered subcutaneously may also be considered as a benefit from the point of view of the quality of foodstuffs (muscle) when compared to certain so-called long acting formulations such as tetracyclines. The benefits of treatment with Micotil include that the animal is treated with an effective antibacterial. In particular, therapeutic levels of the antibacterial tilmicosin are reported to occur in the lung within one hour of administration of Micotil in animals. The product has a relatively long history of use with few questions over its effectiveness in the field. However, evidence based data to demonstrate the benefits of Micotil relative to other authorised antibacterials has not been provided.

Tilmicosin is an antimicrobial substance that is not used in human medicine and resistance in human bacteria to tilmicosin is very low (source: DANMAP). In particular, tilmicosin has no activity against *Salmonella spp.* or *E. coli*, two bacteria often the focus of human food-borne illness concerns. The likelihood of resistance development in these pathogens through exposure to tilmicosin when used for treatment of animals is expected to be negligible.

Risks

When administered by injection, tilmicosin has been fatal in various species, including primates (in monkeys 30 mg/kg bw were shown to be fatal), mainly due to its cardio-toxic effects. Such cardio-toxic effects have also been observed in human beings (mainly after intentional injection but in 2 known cases outside the EU after accidental injection of Micotil). The risk of serious signs of toxicity and death in human beings appear to be linked to plasma concentrations around 5 µg/ml, whereas plasma concentrations of 1-2 µg/ml did not lead to fatalities. Evidence from investigations of 13 occurrences of intentional intramuscular injection suggests that 60% of people who received 10 to 12 ml of Micotil died.

On the basis of a standard human body weight of 60 kg this would equate to 50-60 mg/kg bw. Survival rates are greatly improved by the correct medical intervention. However, it is not possible on the basis of available evidence, to estimate a dose without adverse effects in human beings. Doses of 2-3 ml have been reported to induce adverse effects.

It is evident that accidental injections may occur, but normally the volume injected is low. Very rarely the volume is higher than 1-2 ml and it is improbable that a fatality will occur. Nevertheless, it is necessary to put in practice some measures to reduce the risks of accidental self-injection.

Additional data were provided in relation to 4 studies on the likely action mechanism of tilmicosin on the heart function and on possible remedial measures. In one experiment isolated human cardiac atrial myocites were used to study the L-type Ca channel blocking profile. Tilmicosin was found to dose-dependently reduce ICa amplitude with an IC_{50} value of 26.75 µM. The blockade of this cardiac current is a possible mechanism for the negative inotropic effects that have been observed following the administration of the compound to conscious dogs. Subsequent studies were conducted to determine if intravenous calcium chloride administration reduces or diminishes this toxic cardiovascular effect of tilmicosin. $CaCl_2$ treatment showed a positive inotropic effect on the left ventricular inotropic state after tilmicosin administration in beagle dogs.

The representative of the MAHs further identified a report of accidental injection in humans where $CaCl_2$ had been used as part of the emergency treatment of the patient.

Although the actual role of $CaCl_2$ infusion following tilmicosin exposure in humans is inconclusive because of the limited data available, it is suggested that $CaCl_2$ infusion may help to reverse the induced changes in blood pressure and heart rate in humans.

A related risk is that certain substances, in particular adrenaline (epinephrine), used in standard emergency treatment in human medicine may exacerbate the effects of tilmicosin. Certain others (e.g. dobutamine) have partially countered cardiac effects of tilmicosin in animal experiments (pigs and dogs).

The results of an additional study with administration of epinephrine as a treatment for combating intravenous tilmicosin toxicity in swine strongly suggest that intravenous administration of epinephrine may be contraindicated due to the rate of deaths in the treated group.

Exposure assessment

Before attempting a quantitative risk assessment for human adverse reactions to Micotil, it must be pointed out that any calculations of incidences of reactions in veterinary pharmacovigilance can only be regarded as rough estimates that are influenced by many variables, not the least uncertainties regarding actual doses used in order to estimate the number of animal treatments, and under reporting of actual occurrences of adverse reactions.

Bearing the aforesaid in mind, based on the data provided by the representative of the MAHs on world-wide sales of Micotil since 1999 and the 2 cases of accidental fatal injections in human beings reported to date in the USA, the risk of an accidental human fatality may be estimated as less than 1 per 60 million administrations[1]. This estimate has not been independently verified. As the dosage of the product in adult sheep is typically 1-5 ml and in adult cattle is typically 15-20 ml, it is difficult to accurately estimate the incidence of human reactions or fatalities. In the two accidental fatalities recorded to date the victims were farmers and in both treatment of the adverse reactions involved use of adrenaline (epinephrine), which is considered as contra-indicated in cases of human exposure to tilmicosin. No accidental fatalities due to accidental injection of Micotil have been reported in the EU.

The incidence of accidental injection or accidental self-injection of Micotil has also been estimated by the representative of the MAHs as 1.6 per million administrations, with an overall incidence of accidental exposure of a human being of 3 exposures per million administrations. In total 520 human exposures were reported since 1999, of which 509 were accidental. Of these 509 reports, 214 cases related to non-injection exposures, and 295 to injection exposures, with minor needle scratches being the most common.

[1] Calculation of number of administrations (doses) based on a 10 mg/kg BW dose, 90% in cattle (250 kg BW) and 10% in sheep (30 kg BW) for the USA. For the EU the average bovine weight was put on 150 kg (90% of the sales) whereas the average ovine weight was kept at 30 kg.

It must be noted that systems for properly recording suspected adverse reactions may not be in existence in every country in the world where the product is marketed. Also the situation is dynamic and may change as new cases arise.

Qualitative risk assessment

The CVMP concurs with the representative of the MAHs that 'the risk of fatal outcome as a result of an accidental injection/self-injection can be related to the following factors: dose, unrestrained animals, unprotected needles attached to a loaded syringe, working in isolation, the lack of accessible product information for emergency or health care professional to determine suitable treatments'.

Given the diversity of farming conditions throughout the different EU Member States concerned by the referral, the various capabilities of farmers in the EU Member States concerned, as well as the recent trends in farming of more suckler animals and scarcity of labour in some EU Member States, the CVMP does not concur with the view of the representative of the MAHs that **all** 'professional' farmers may be regarded as experienced and competent.

Recognising that farming practices in the USA, where the accidental fatalities were reported, differ significantly from farming practices in the EU different risk management approaches between the USA and the EU may be required.

Other aspects relevant to the risk assessment include the fact that the use in cattle probably carries a higher risk of serious adverse effects in humans than would be the case in sheep due to the fact that adult cattle may be more physically threatening and the volumes used are higher. By contrast it seems probable that the risk of non-fatal effects in humans following use in sheep would be higher than in cattle due to the fact that sheep require a lower dose and the product may be widely used in such animals. Improvements to the advice to physicians and access to appropriate medical information following poisoning are also likely to reduce the risk of severe effects as more effective hospital care might be available. However, it is possible that if the lay use of the product were to continue, any improvements in medical advice and hospital care might be of academic use as the appropriate medical intervention could be too late.

Discussion of risk management options

A number of risk management options considered by the CVMP are detailed below. Other combinations of measures would theoretically be possible, but would not present significant additional benefits to risk management, and they are therefore not discussed.

1. Withdrawal of the product from the market in the EU

The withdrawal of Micotil from the market in the EU has been considered in the risk analysis conducted by the CVMP and would reduce the risk of human fatalities or any human adverse reactions to zero.

In view of the benefits afforded by the product as set out above and on the basis of the evidence provided by the representative of the MAHs the CVMP is of the opinion that this approach is however not proportionate. It is appreciated that this action would reduce the therapeutic armoury available for the effective treatment of diseases in animals.

2. Maintaining the status quo

A theoretical risk management option would be to maintain the status quo with respect to the divergence in the different EU Member States of user safety warnings, and additional safety measures, such as limitations of volume to be held per syringe, or restriction to use by veterinarians.

In the opinion of the CVMP, this is not a solution in view of the potential risk of accidental fatalities in human beings.

3. Recommendation of harmonised, stringent EU user safety warnings including advice to the physician on appropriate treatment, and appropriate educational measures for users, without further restrictions

Harmonised, stringent user safety warnings would include:

- Clear warning that injection of the product in human beings has been associated with fatalities;
- Instructions for safe use of the product (use different needles for loading a syringe and injecting into an animal, always uncouple syringe from needle during transport);
- Instructions to properly restrain animals (the one treated and others in the vicinity);
- Instructions never to work alone;
- Recommendation to provide the physician with the vial or the package leaflet in case of accidental injection;
- Note to the physician in the package leaflet and SPC detailing the known effects of Micotil in human beings, treatments to be avoided and substances that may partially counter certain effects of Micotil, including telephone numbers of national poison centres.

Appropriate educational measures targeted at users (mainly the agricultural community) would be undertaken by the MAHs.

This option bears the following inherent risks:

- The educational measures for the user are a prerequisite to ensure appropriate adherence to the safety warnings. The CVMP is aware that educational measures are not likely to be 100% effective in reaching the intended target audience, the users, and will require repetition at regular intervals in order to achieve a high level of awareness. The risk of failure of the proposed measure is considered as very real;
- The users of the products, though a number may be highly qualified and experienced in handling farm animals, are likely to be very divergent in respect to experience in handling and administration of medicines of high toxic potential. A significant number of such users is likely to not fully understand the implications of the warnings and:
    - may not fully apply the measures intended to ensure their personal safety (i.e. the warning not to work alone is likely to be ignored; users may fail to detach the needle from the syringe containing the product and not fully understand the risks of accidental injection);
    - improperly store the product, potentially leading to easier availability for misuse and abuse;
    - may inappropriately use any product remaining following treatment of the original animal(s) at a later time point with consequential risks.

4. Recommendation of harmonised, stringent EU user safety warnings including advice to the physician on appropriate treatment, restriction of use to veterinary surgeons and other suitably qualified persons (as judged by the veterinary surgeons), and appropriate educational measures for users

Harmonised, stringent user safety warnings would include:

- Clear warning that injection of the product in human beings has been associated with fatalities;
- Instructions for safe use of the product (use different needles for loading a syringe and injecting into an animal, always uncouple syringe from needle during transport);
- Instructions to properly restrain animals (the one treated and others in the vicinity);
- Instructions never to work alone;
- Recommendation to provide the physician with the vial or the package leaflet in case of accidental injection;
- Note to the physician in the package leaflet and SPC detailing the known effects of Micotil in human beings, treatments to be avoided and substances that may partially counter certain effects of Micotil, including telephone numbers of national poison centres.

Some form of documentation would be required to note the dispensing veterinary surgeon's decision to consider a person suitably qualified, where the suitably qualified person also acknowledges

understanding of the risks afforded by the product, the implications with respect to personal safety and regarding safe storage.

Appropriate educational measure targeted at users (veterinary surgeons and the agricultural community) would be undertaken by the MAHs.

This option bears the following inherent risks:

- The CVMP is aware that educational measures are not likely to be 100% effective in reaching all intended targets and will require repetition at regular intervals in order to achieve a high level of awareness. However, the fact that the attending veterinary surgeon needs to ascertain the competence of the user, with both parties signing a form, is likely to minimise the risk of failure of this part of the measures;
- While with this option the users of Micotil are more likely to understand the implications of the recommended warnings, a risk, though arguably lower than for option number 3, remains that:
    - the recommended measures intended to ensure their personal safety are not fully applied (i.e. the warning not to work alone is likely to be ignored; users may fail to detach the needle from the syringe containing the product and not fully understand the risks of accidental injection);
    - the product is not stored properly, potentially leading to easier availability for misuse and abuse;
    - any product remaining following treatment of the original animal(s) may be inappropriately used at a later time point with consequential risks.

5. Recommendation of harmonised, stringent EU user safety warnings including advice to the physician on appropriate treatment, restriction of use to veterinary surgeons only, and appropriate educational measures for users

Harmonised, stringent user safety warnings would include:

- Clear warning that injection of the product in human beings has been associated with fatalities;
- Instructions for safe use of the product (use different needles for loading a syringe and injecting into an animal, always uncouple syringe from needle during transport);
- Instructions to properly restrain animals (the one treated and others in the vicinity);
- Instructions never to work alone;
- Recommendation to provide the physician with the vial or the package leaflet in case of accidental injection;
- Note to the physician in the package leaflet and SPC detailing the known effects of Micotil in human beings, treatments to be avoided and substances that may partially counter certain effects of Micotil, including telephone numbers of national poison centres.

The use of the product would be restricted to veterinary surgeons only.

Appropriate educational measures for veterinary surgeons in practice would be required of the MAH to ensure awareness of veterinary surgeons to the changed evaluation of the product.

This option bears the following inherent risk:

- A residual risk remains that the veterinary surgeon may not fully comply with the recommended measures intended to ensure their personal safety (e.g. the user may fail to detach the needle from the syringe containing the product).

Overall, the CVMP considers the risks inherent to this option would be the lowest. Veterinary surgeons have specific training in drug safety, clinical medicine, animal husbandry, restraining and handling of animals. They tend to be physically active and involved in handling animals every day. They are trained for and used to appropriate storage of potentially lethal products.

6. Additional recommendation to any of the options 3. to 5. regarding limitation of the volume of Micotil to be held per syringe or of maximum pack size or re-formulation of the product

The CVMP did not consider it necessary to recommend a limitation of the amount of Micotil to be held per syringe. Such a volume restriction would necessitate additional administrations to the same animal. While reducing the maximum amount available for accidental injection of the user, this measure would increase the chances for accidental exposure of human beings. This measure would additionally increase the stress to the treated animals by longer duration of restraint and multiple injections and reduce the benefits of the product in respect to a higher number of injection sites. In addition this measure would bear a high risk of being ignored.

Considering the recommendation of the Committee to restrict use to veterinary surgeons only, restriction of maximum pack size is not relevant, as the product will remain in the care of the veterinary surgeon.

The CVMP did not consider it feasible or appropriate to recommend the re-formulation of the product to lower strength. It noted that a lower strength product would firstly lead to an increase in the number of administrations necessary to achieve a therapeutic dose. Secondly, re-formulation would necessitate new quality, safety and efficacy studies, which might not be feasible. Thirdly, re-formulation to a lower strength product might not lead to a tangible risk reduction as the dose causing adverse effects in human beings is not known and is expected to vary depending on the physical condition of the individual.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS:

Whereas

- the Committee considered the referral made under Article 35 of Directive 2001/82/EC in the interest of the Community regarding user safety for national marketing authorisations for Micotil or variations of that name as listed in Annex I of the opinion;

- the Committee assessed the information provided by the Marketing Authorisation Holders in response to the list of questions agreed by the Committee on 16 June 2004 and the additional information provided on 12 July 2005;

- the Committee unanimously considered it necessary that the user safety warnings for the products concerned be harmonised throughout the EU in order to ensure appropriate user safety, in consideration of the referral question whether the wording with regard to the safety of users of the Micotil product literature should be harmonised;

- the Committee, having considered the referral question whether the wording with regard to the safety of users of the Micotil product literature should be harmonised in respect of a restriction to use by veterinary surgeons only, by majority considered that the condition of use be harmonised to 'For use by veterinary surgeons only'; this condition was considered essential for the safe use of the veterinary medicinal product;

- the Committee, having considered the referral question whether the wording of the Micotil product literature should be harmonised with regard to the volume to deliver per syringe with regard to the safety of users, unanimously did not consider such a restriction to be an appropriate measure in order to ensure appropriate user safety throughout the EU;

the CVMP recommends by a majority of 18 out of 27 votes that the warnings relative to user safety of the nationally granted Marketing Authorisations be harmonised and that the conditions of use be harmonised to 'For use by veterinary surgeons only'; the revised aspects of the Summary of Product Characteristics are set out in Annex III and the conditions considered essential for the safe use of the product, as referred to in Article 36(4) of Directive 2001/82/EC as amended, are set out in Annex IV.

ANNEX III

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS

Under paragraph 4.4 "Special warnings for each target species"

Sheep

Do not inject lambs weighing less than 15 kg, since there is a real risk of overdose toxicity. Accurate weighing of lambs is important to avoid overdosage. The use of a 2 ml or smaller syringe will facilitate accurate dosing.

Under paragraph 4.5 "Special precautions for use"

"Special precautions to be taken by the person administering the medicinal product to animals"

Operator Safety Warnings:

A statement in a frame with yellow background colour, saying:

INJECTION OF THIS DRUG IN HUMANS CAN BE FATAL – EXERCISE EXTREME CAUTION TO AVOID ACCIDENTAL SELF-INJECTION AND FOLLOW THE ADMINISTRATION INSTRUCTIONS AND THE GUIDANCE BELOW, PRECISELY

- This product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with Micotil with the needle attached. The needle should be connected to the syringe only when filling the syringe or administering the injection. Keep the syringe and needle separate at all other times.
- Do not use automatic injection equipment.
- Ensure that animals are properly restrained, including those in the vicinity.
- Do not work alone when using Micotil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take the vial or the package insert with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:

- Avoid contact with eyes.
- May cause sensitisation by skin contact. Wash hands after use.

NOTE TO THE PHYSICIAN

INJECTION OF THIS DRUG IN HUMANS HAS BEEN ASSOCIATED WITH FATALITIES.

The cardiovascular system is the target of toxicity, and this toxicity may be due to calcium channel blockade. Administration of intravenous calcium chloride should only be considered if there is positive confirmation of exposure to tilmicosin.

In dog studies, tilmicosin induced a negative inotropic effect with consequent tachycardia, and a reduction in systemic arterial blood pressure and arterial pulse pressure.

DO NOT GIVE ADRENALIN OR BETA-ADRENERGIC ANTAGONISTS SUCH AS PROPRANOLOL.

In pigs, tilmicosin-induced lethality is potentiated by adrenalin.

In dogs, treatment with intravenous calcium chloride showed a positive effect on the left ventricular inotropic state and some improvements in vascular blood pressure and tachycardia.

Pre-clinical data and an isolated clinical report suggest that calcium chloride infusion may help to reverse tilmicosin induced changes in blood pressure and heart rate in humans.

Administration of dobutamine should also be considered due to its positive inotropic effects although it does not influence tachycardia.

As tilmicosin persists in tissues for several days, the cardiovascular system should be closely monitored and supportive treatment provided.

Physicians treating patients exposed to this compound are advised to discuss clinical management with the National Poison Information Service on: (*indicate here the telephone number of the centre).*

Under paragraph 4.9 "Amounts to be administered and administration route"

Method of administration:
Withdraw the required dose from the vial and remove the syringe from the needle. If a group of animals is to be treated, leave the needle in the vial as a draw-off needle for subsequent doses. Restrain the animal and insert a separate needle subcutaneously into the injection site. Injection in a fold of skin over the rib cage behind the shoulder is suggested. Connect the syringe to the needle and inject into the base of the skin fold. Do not inject more than 20 ml per injection site.

Under paragraph 5.1 "Pharmacodynamic properties"

Following oral or parenteral administration of tilmicosin the main target organ for toxicity is the heart. The primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotrophy). Cardiovascular toxicity may be due to calcium channel blockade.

In dogs, $CaCl_2$ treatment showed a positive effect on the left ventricular inotrophic state after tilmicosin administration and some changes in vascular blood pressure and heart rate.

Dobutamine partially offset the negative inotrophic effects induced by tilmicosin in dogs. Beta adrenergic antagonists such as propanolol exacerbated the negative inotrophy of tilmicosin in dogs.

In pigs, intramuscular injection of 10 mg tilmicosin/kg caused increased respiration, emesis and convulsions; 20 mg/kg resulted in mortality in 3 of 4 pigs, and 30 mg/kg caused the death of all 4 pigs tested. Intravenous injection of 4.5 to 5.6 mg tilmicosin/kg followed by intravenous injection of 1 ml epinephrine (1/1000) 2 to 6 times resulted in death of all 6 injected pigs. Pigs given 4.5 to 5.6 mg tilmicosin/kg intravenously with no epinephrine all survived. These results suggest that intravenous epinephrine may be contraindicated.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

For use by veterinary surgeons only.

Furthermore the revised aspects of the Summary of Product Characteristics should be implemented in the labelling and product leaflet as set out below.

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

OUTER CARTON –ALL AUTHORISED PACK SIZES

7. METHOD AND ROUTE OF ADMINISTRATION

Method of administration:
Withdraw the required dose from the vial and remove the syringe from the needle. If a group of animals is to be treated, leave the needle in the vial as a draw-off needle for subsequent doses. Restrain the animal and insert a separate needle subcutaneously into the injection site. Injection in a fold of skin over the rib cage behind the shoulder is suggested. Connect the syringe to the needle and inject into the base of the skin fold. Do not inject more than 20 ml per injection site.

Sheep
Do not inject lambs weighing less than 15 kg, since there is a real risk of overdose toxicity. Accurate weighing of lambs is important to avoid overdosage. The use of a 2 ml or smaller syringe will facilitate accurate dosing.

9. SPECIAL WARNINGS

Operator Safety Warnings:

A statement in a frame with yellow background colour, saying:

INJECTION OF THIS DRUG IN HUMANS CAN BE FATAL – EXERCISE EXTREME CAUTION TO AVOID ACCIDENTAL SELF-INJECTION AND FOLLOW THE ADMINISTRATION INSTRUCTIONS AND THE GUIDANCE BELOW, PRECISELY

- This product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with Micotil with the needle attached. The needle should be connected to the syringe only when filling the syringe or administering the injection. Keep the syringe and needle separate at all other times.
- Do not use automatic injection equipment.
- Ensure that animals are properly restrained, including those in the vicinity.
- Do not work alone when using Micotil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take the vial or the package leaflet with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:
- Avoid contact with eyes
- May cause sensitisation by skin contact. Wash hands after use

NOTE TO THE PHYSICIAN:
Please see inside part of label or package leaflet for details

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only to be supplied only on veterinary prescription.

For use by veterinary surgeons only.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

IMMEDIATE (VIAL) LABEL – ALL AUTHORISED PACK SIZES

7. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

9. SPECIAL WARNINGS

On the outside of the peel-back label

Operator Safety Warnings:

A statement in a frame with yellow background colour, saying:

INJECTION OF THIS DRUG IN HUMANS CAN BE FATAL – EXERCISE EXTREME CAUTION TO AVOID ACCIDENTAL SELF-INJECTION AND FOLLOW THE ADMINISTRATION INSTRUCTIONS AND THE GUIDANCE BELOW, PRECISELY

- This product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with Micotil 300 with the needle attached. The needle should be connected to the syringe only when filling the syringe or administering the injection. Keep the syringe and needle separate at all other times.
- Do not use automatic injection equipment.
- Ensure that animals are properly restrained, including those in the vicinity.
- Do not work alone when using Micotil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take this vial or the package leaflet with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:

- Avoid contact with eyes.
- May cause sensitisation by skin contact. Wash hands after use.

NOTE TO THE PHYSICIAN:
Please see inside part of label or package leaflet for details.

On the inside of the peel-back label

NOTE TO THE PHYSICIAN

INJECTION OF THIS DRUG IN HUMANS HAS BEEN ASSOCIATED WITH FATALITIES.

The cardiovascular system is the target of toxicity, and this toxicity may be due to calcium channel blockade. Administration of intravenous calcium chloride should only be considered if there is positive confirmation of exposure to tilmicosin

In dog studies, tilmicosin induced a negative inotropic effect with consequent tachycardia, and a reduction in systemic arterial blood pressure and arterial pulse pressure.

DO NOT GIVE ADRENALIN OR BETA-ADRENERGIC ANTAGONISTS SUCH AS PROPRANOLOL.

In pigs, tilmicosin-induced lethality is potentiated by adrenalin.

In dogs, treatment with intravenous calcium chloride showed a positive effect on the left ventricular inotropic state and some improvements in vascular blood pressure and tachycardia.

Pre-clinical data and an isolated clinical report suggest that calcium chloride infusion may help to reverse tilmicosin induced changes in blood pressure and heart rate in humans.

Administration of dobutamine should also be considered due to its positive inotropic effects although it does not influence tachycardia.

As tilmicosin persists in tissues for several days, the cardiovascular system should be closely monitored and supportive treatment provided.

Physicians treating patients exposed to this compound are advised to discuss clinical management with the National Poisons Information Service on: (*indicate here the telephone number of the centre).*

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only to be supplied only on veterinary prescription.

For use by veterinary surgeons only.

B. PACKAGE LEAFLET

8. DOSAGE FOR EACH SPECIES, ROUTE(S) OF ADMINISTRATION AND METHOD OF ADMINISTRATION

Method of administration:

Withdraw the required dose from the vial and remove the syringe from the needle. If a group of animals is to be treated, leave the needle in the vial as a draw-off needle for subsequent doses. Restrain the animal and insert a separate needle subcutaneously into the injection site. Injection in a fold of skin over the rib cage behind the shoulder is suggested. Connect the syringe to the needle and inject into the base of the skin fold. Do not inject more than 20 ml per injection site.

9. ADVICE ON CORRECT ADMINISTRATION

Sheep

Do not inject lambs weighing less than 15 kg, since there is a real risk of overdose toxicity. Accurate weighing of lambs is important to avoid overdosage. The use of a 2 ml or smaller syringe will facilitate accurate dosing.

12. SPECIAL WARNING(S)

Operator Safety Warnings:

A statement in a frame with yellow background colour, saying:

INJECTION OF THIS DRUG IN HUMANS CAN BE FATAL – EXERCISE EXTREME CAUTION TO AVOID ACCIDENTAL SELF-INJECTION AND FOLLOW THE ADMINISTRATION INSTRUCTIONS AND THE GUIDANCE BELOW, PRECISELY

- This product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with Micotil with the needle attached. The needle should be connected to the syringe only when filling the syringe or administering the injection. Keep the syringe and needle separate at all other times.
- Do not use automatic injection equipment.
- Ensure that animals are properly restrained, including those in the vicinity.
- Do not work alone when using Micotil.
- In case of human injection SEEK IMMEDIATE MEDICAL ATTENTION and take this package leaflet or the vial with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:

- Avoid contact with eyes.
- May cause sensitisation by skin contact. Wash hands after use.

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15. OTHER INFORMATION

Following oral or parenteral administration of tilmicosin the main target organ for toxicity is the heart. The primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotrophy). Cardiovascular toxicity may be due to calcium channel blockade.

In dogs, $CaCl_2$treatment showed a positive effect on the left ventricular inotrophic state after tilmicosin administration and some changes in vascular blood pressure and heart rate.

Dobutamine partially offset the negative inotrophic effects induced by tilmicosin in dogs. Beta adrenergic antagonists such as propanolol exacerbated the negative inotrophy of tilmicosin in dogs.

In pigs, intramuscular injection of 10 mg tilmicosin/kg caused increased respiration, emesis and convulsions; 20 mg/kg resulted in mortality in 3 of 4 pigs, and 30 mg/kg caused the death of all 4 pigs tested. Intraveneous injection of 4.5 and 5.6 mg tilmicosin/kg followed by intravenous injection of 1 ml epinephrine (1/1000) 2 to 6 times resulted in death of all 6 injected pigs. Pigs given 4.5 and 5.6 mg tilmicosin/kg intravenously with no epinephrine all survived. These results suggest that intravenous epinephrine may be contraindicated.