ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZACTRAN 150 mg/ml solution for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:

Active substance:
Gamithromycin 150 mg

Excipient:
Monothioglycerol 1 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and pigs.

4.2 Indications for use, specifying the target species

Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. The presence of the disease in the herd should be established before metaphylactic use.

Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis.*

4.3 Contraindications

Do not use in case of hypersensitivity to macrolide antibiotics or to any of the excipients.
Do not use this veterinary medicinal product simultaneously with other macrolides or lincosamides (see section 4.8).

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Use of the veterinary medicinal product should be based on susceptibility testing and take into account official and local policies on the use of antimicrobials in farm animals.

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

People with known hypersensitivity to the macrolide class should avoid contact with the veterinary medicinal product. Gamithromycin may cause irritation to eyes and/or skin.
Avoid contact with skin or eyes. If eye exposure occurs, flush eyes immediately with clean water. If skin exposure occurs, wash the affected area immediately with clean water.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

During clinical trials transient injection site swellings were observed.

- Very commonly, visible injection site swellings may develop in cattle associated with occasional, slight pain evident for one day. The swellings typically resolve within 3 to 14 days but may persist in some animals for up to 35 days after treatment.
- Commonly, mild to moderate injection site swelling may develop in pigs. These local reactions are transient, and typically resolve within 2 days.

The frequency of adverse reactions is defined using the following convention:

- Very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- Common (more than 1 but less than 10 animals in 100 animals)
- Uncommon (more than 1 but less than 10 animals in 1,000 animals)
- Rare (more than 1 but less than 10 animals in 10,000 animals)
- Very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Based on laboratory animal data, gamithromycin has not produced any evidence of selective developmental or reproductive effects. The safety of gamithromycin during pregnancy and lactation has not been evaluated in cattle and pigs. Use only according to the risk/benefit assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Cross resistance may occur with other macrolides.
Avoid simultaneous administration of antimicrobials with a similar mode of action such as other macrolides or lincosamides.

4.9 Amounts to be administered and administration route

A single dose of 6 mg gamithromycin/kg body weight (equivalent to 1 ml/25 kg body weight) into the neck. To ensure correct dose, body weight should be determined as accurately as possible to avoid underdosing.

Cattle
Subcutaneous injection. For treatment of cattle over 250 kg body weight, divide the dose so that no more than 10 ml are injected at a single site.

Pigs
Intramuscular injection. The injection volume should not exceed 5 ml per injection site.

The cap may be safely punctured up to 60 times. For multiple vial entry, an automatic dosing device is recommended to avoid excessive broaching of the stopper.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Clinical studies have demonstrated the wide margin of safety for gamithromycin injection in the target species. In young adult cattle and pig studies, gamithromycin was administered by injection at 6, 18, and 30 mg/kg (1, 3, and 5 times the recommended dose) and repeated three times at 0, 5 and 10 days (three times the recommended duration of use). Injection site reactions were noted in a dose related manner.

4.11 Withdrawal period

Meat and offal:
Cattle: 64 days.
Pigs: 16 days

Not authorised for use in lactating animals producing milk for human consumption.
Do not use in pregnant cows or heifers which are intended to produce milk for human consumption, within 2 months of expected parturition.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides
ATC vet code: QJ01FA95.

5.1 Pharmacodynamic properties

Gamithromycin is an azalide, 15-membered semisynthetic macrolide class antibiotic with uniquely positioned alkylated nitrogen at 7a-position of the lactone ring. This special chemistry facilitates rapid absorption at physiological pH and a long duration of action at the target tissue, the lung.
Macrolides in general have both bacteriostatic and bactericidal action mediated through disruption of bacterial protein synthesis. Macrolides inhibit bacterial protein biosynthesis by binding to the 50S ribosomal subunit and by preventing peptide chain elongation. The *in vitro* data show that gamithromycin acts in a bactericidal manner. The broad spectrum antimicrobial activity of gamithromycin includes *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, *Actinobacillus pleuropneumoniae* and *Haemophilus parasuis*, the bacterial pathogens most commonly associated with BRD and SRD. The MIC and MBC data are reported from a representative sample of isolates from field materials within different EU geographic areas.

Cattle	MIC_{90s}	MBC_{90s}
	µg/ml	
Mannheimia haemolytica	0.5	1
Pasteurella multocida	1	2
Histophilus somni	1	2
Pigs	MIC_{90s}	MBC_{90s}
	µg/ml	
Actinobacillus pleuropneumoniae	4	4
Pasteurella multocida	1	2
Haemophilus parasuis	0.5	0.5

Three mechanisms are generally considered responsible for resistance to the macrolide class of compounds. This is often referred to as MLS_B resistance as it affects macrolides, lincosamides and streptogramins. The mechanisms involve the alteration of the ribosomal target site, the utilization of active efflux mechanism and the production of inactivating enzymes.

5.2 Pharmacokinetic particulars

Cattle
Gamithromycin administered subcutaneously into the neck of cattle at a single dose of 6 mg/kg body weight, resulted in rapid absorption with peak plasma concentrations observed after 30 to 60 min with a long plasma half-life (> 2 days). The bioavailability of the compound was > 98 % with no gender differences. The volume of distribution at steady-state was 25 l/kg. Gamithromycin levels in lung reached a maximum in less than 24 hr, with lung-to-plasma ratio of > 264 indicating that gamithromycin was absorbed rapidly into the target tissue for BRD.

In vitro plasma protein binding studies determined that the mean concentration of the free active substance was 74 %. Biliary excretion of the unchanged drug substance was the major route of elimination.

Pigs
Gamithromycin administered intramuscularly in pigs at single dose of 6 mg/kg body weight, resulted in rapid absorption with peak plasma concentrations observed after 5 to 15 min, with a long plasma half-life (about 4 days). The bioavailability of gamithromycin was > 92 %. The compound is absorbed rapidly into the target tissue for SRD. Accumulation of gamithromycin in the lung has been demonstrated by high and sustained concentrations in the lung and bronchial fluid which far exceed those in blood plasma. The volume of distribution at steady-state was approximately 39 l/kg. *In vitro* plasma protein binding studies determined that the mean concentration of the free active drug was 77 %. Biliary excretion of the unchanged drug was the major route of elimination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monothioglycerol
Succinic Acid
Glycerol Formal

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product should not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Type 1 glass vial of 50, 100, 250 or 500 ml with a chlorobutyl rubber stopper and an aluminium cap.
Polypropylene vial of 100, 250 or 500 ml with a chlorobutyl rubber stopper and an aluminium cap.

Cardboard box containing 1 vial of 50, 100, 250 or 500 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MERIAL
29, avenue Tony Garnier
F-69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/082/001
EU/2/08/082/002
EU/2/08/082/003
EU/2/08/082/004
EU/2/08/082/005
EU/2/08/082/006
EU/2/08/082/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24/07/2008
Date of last renewal: 15/07/2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY OR USE

C. STATEMENT OF THE MRLs

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

MERIAL
4, Chemin du Calquet
31057 Toulouse Cedex
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY OR USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

The active substance in ZACTRAN 150 mg/ml solution for injection for cattle and pigs is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Gamithromycin	Gamithro-mycin	Bovine	20 µg/kg 200 µg/kg 100 µg/kg	Fat Liver Kidney	Not for use in animals producing milk for human consumption	Anti-infectious agents / Antibiotics
		Porcine	100 µg/kg 100 µg/kg 100µg/kg 300 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney	NO ENTRY	

The excipients listed in section 6.1 of the SPC are allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The periodic safety update report (PSUR) cycle should be re-started for submission of 6- monthly reports (covering all authorised presentations of the product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at 3 yearly intervals.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZACTRAN 150 mg/ml solution for injection for cattle and pigs
gamithromycin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

1 ml contains 150 mg of gamithromycin,

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml
250 ml
500 ml

5. TARGET SPECIES

Cattle, pigs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Cattle: Subcutaneous use
Pigs: Intramuscular use
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: Cattle: 64 days. Pigs: 16 days
Not authorised for use in lactating animals producing milk for human consumption.
Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP
Once opened, use by ….

11. SPECIAL STORAGE CONDITIONS

Not applicable.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read the package leaflet.

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

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

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MERIAL
29 avenue Tony Garnier
F-69007 Lyon
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/082/001
EU/2/08/082/002
EU/2/08/082/003
EU/2/08/082/004
EU/2/08/082/005
EU/2/08/082/006
EU/2/08/082/007

17. MANUFACTURER'S BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

VIAL 100 ml, 250 ml, 500 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZACTRAN 150 mg/ml solution for injection for cattle and pigs
gamithromycin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

1 ml contains 150 mg of gamithromycin,

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml
250 ml
500 ml

5. TARGET SPECIES

Cattle, pigs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

SC (cattle) IM (pigs)
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: Cattle: 64 days. Pigs: 16 days
Not authorised for use in animals producing milk for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP
Once opened, use by …

11. SPECIAL STORAGE CONDITIONS

Not applicable.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Read the package leaflet before use.

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

For animal treatment only - To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MERIAL
29 avenue Tony Garnier
F-69007 Lyon
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/082/001
EU/2/08/082/002
EU/2/08/082/003
EU/2/08/082/004
EU/2/08/082/005
EU/2/08/082/006

17. MANUFACTURER'S BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

VIAL 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZACTRAN 150 mg/ml solution for injection for cattle and pigs
gamithromycin

2. QUANTITY OF THE ACTIVE SUBSTANCE

1 ml contains 150 mg of gamithromycin

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

50 ml

4. ROUTE OF ADMINISTRATION

SC (cattle), IM (pigs)

5. WITHDRAWAL PERIOD

Withdrawal period: Meat and offal: Cattle: 64 days. Pigs: 16 days
Not authorised for use in animals producing milk for human consumption.

6. BATCH NUMBER

Lot

7. EXPIRY DATE

EXP
Once opened, use by ….

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR
ZACTRAN 150 mg/ml solution for injection for cattle and pigs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
MERIAL
29 avenue Tony Garnier
F-69007 Lyon
France

Manufacturer responsible for batch release:
MERIAL
4, Chemin du Calquet
F-31057 Toulouse Cedex
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZACTRAN 150 mg/ml solution for injection for cattle and pigs
Gamithromycin

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

1 ml contains
Active substance: 150 mg of gamithromycin
Excipients: 1 mg of monothioglycerol
Colourless to pale yellow solution.

4. INDICATIONS

Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.
The presence of the disease in the herd should be established before metaphylactic use.

Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Haemophilus parasuis.*

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to a certain type of antibiotics called macrolides or to any of the excipients.
Do not use this veterinary medicinal product simultaneously with other macrolides or antibiotics known as lincosamides.

6. ADVERSE REACTIONS

During clinical trials transient injection site swellings were observed.

- Very commonly, visible injection site swellings may develop in cattle associated with occasional, slight pain evident for one day. The swellings typically resolve within 3 to 14 days but may persist in some animals for up to 35 days after treatment.
- Commonly, mild to moderate injection site swelling may develop in pigs. These local reactions are transient and typically resolve within 2 days.

The frequency of adverse reactions is defined using the following convention:
- Very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- Common (more than 1 but less than 10 animals in 100 animals)
- Uncommon (more than 1 but less than 10 animals in 1,000 animals)
- Rare (more than 1 but less than 10 animals in 10,000 animals)
- Very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinarian.

7. TARGET SPECIES

Cattle and pigs.

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

A single dose of 6 mg gamithromycin/kg body weight (equivalent to 1 ml/25 kg body weight) into the neck.

Cattle: **subcutaneous** injection. For treatment of cattle over 250 kg body weight, divide the dose so that no more than 10 ml are injected at a single site.

Pigs: **intramuscular** injection. The injection volume should not exceed 5 ml per injection site.

The cap may be safely punctured up to 60 times. For multiple vial entry, an automatic dosing device is recommended to avoid excessive broaching of the stopper.

9. ADVICE ON CORRECT ADMINISTRATION

To ensure correct dose, body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

Meat and offal: Cattle: 64 days. Pigs: 16 days
Not authorised for use in lactating animals producing milk for human consumption.
Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the vial after EXP.
Shelf-life after first opening the container: 28 days.

12. SPECIAL WARNINGS

Special precautions for use in animals:
Use of the veterinary medicinal product should be based on susceptibility testing and take into account official and local policies on the use of antimicrobials in farm animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to the macrolide class should avoid contact with the veterinary medicinal product.

Gamithromycin may cause irritation to eyes and/or skin. Avoid contact with skin or eyes. If eye exposure occurs, flush eyes immediately with clean water. If skin exposure occurs, wash the affected area immediately with clean water.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Pregnancy and lactation:
The safety of gamithromycin during pregnancy and lactation has not been evaluated in cattle and pigs. Use according to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Cross resistance may occur with other macrolides.
Avoid simultaneous administration of antimicrobials with a similar mode of action such as other macrolides or lincosamides.

Overdose:
In young adult cattle and pig studies, gamithromycin was administered by injection at 6, 18, and 30 mg/kg (1, 3, and 5 times the recommended dose) and repeated three times at 0, 5 and 10 days (three times the recommended duration of use). Injection site reactions were noted in a dose related manner.

Incompatibilities:
ZACTRAN should not be mixed with other medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

15. OTHER INFORMATION

Cardboard box containing 1 vial of 50, 100, 250 or 500 ml.
Not all pack sizes may be marketed.