ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Butafosal 100 mg/ml + 0.05 mg/ml solution for injection for cattle, horses and dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Butaphosphan	100 mg
Cyanocobalamin (Vitamin $_{B12}$)	0.05mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl Alcohol (E1519)	10.5 mg
Sodium Hydroxide (for pH adjustment)	-
Water for injection	-

Clear pink to red colored solution, free from visible particulate matter

3. CLINICAL INFORMATION

3.1 Target species

Cattle, horses and dogs

3.2 Indications for use, for each target species

All target species:

- Supportive treatment and prevention of hypophosphatemia and/or cyanocobalamin (vitamin B12) deficiency.

Cattle:

- Supportive treatment to restore rumination following surgical treatment of displaced abomasum associated with secondary ketosis.
- Complementary treatment of parturient paresis in addition to Ca/Mg therapy.
- Prevention of ketosis development, if administered before calving.

Horses:

Adjunctive therapy in horses suffering from muscular exhaustion.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Intravenous administration should be done very slowly since cases of circulatory shock may be associated with too rapid injection.

In dogs suffering from chronic renal insufficiency the veterinary medicinal product should only be used according to the benefit-risk assessment by the responsible veterinarian.

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

Accidental self-injection of this veterinary medicinal product may cause adverse effects.
Self-injection should be avoided.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause skin and eye irritation.
Avoid contact with skin and eyes.
In case of accidental exposure, rinse the affected area thoroughly with water.

The active substance cyanocobalamin and the excipient benzyl alcohol may cause hypersensitivity reactions.
People with known hypersensitivity to these ingredients should avoid contact with the veterinary medicinal product.
If you develop symptoms following exposure, such as a skin rash, seek medical advice and show the package leaflet or the label to the physician.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle, horses and dogs:

Rare (1 to 10 animals / 10,000 animals treated):	Injection site pain[1]

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Circulatory shock[2]

[1]Has been reported following subcutaneous administration in dogs.
[2]In cases where rapid intravenous infusion has occurred.

Reporting adverse events is important. It allows continuous safety monitoring of veterinary medicinal products. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system.
See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in mares and bitches.

Pregnancy and lactation:
Cows:
Can be used during pregnancy and lactation.

Horses and dogs:
Laboratory studies in rats have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Cattle and horses:
Intravenous use.

Dogs:
Intravenous, intramuscular and subcutaneous use.

It is recommended that the solution is warmed to body temperature before administration.
The dose depends on the animal's body weight (bw) and condition.

Species	Dose butafosfan (mg/kg bw)	Dose cyanocobalamin (mg/kg bw)	Dose volume of the veterinary medicinal product	Route of administration
Cattle Horses	5–10	0.0025–0.005	5–10 ml/100 kg	i.v.
Dogs	10–15	0.005–0.0075	0.1–0.15 ml/kg	i.v., i.m., s.c.

For the supportive treatment of secondary ketosis in cows, the recommended dose should be administered on three consecutive days.
For the prevention of ketosis in cows, the recommended dose should be administered on three consecutive days within the period of 10 days before expected calving.
For other indications, treatment should be repeated as necessary.

The rubber stopper of the vial may be safely punctured up to 40 times with 18 gauge needle. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used to avoid excessive puncturing of the closure.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

No adverse effect was reported after intravenous administrations up to 5 times the recommended dose in cattle.
Except transient slight swelling at the injection site, no other adverse effect was reported after subcutaneous administrations up to 5 times the recommended dose in dogs.
No overdose data are available for dogs after intravenous and intramuscular administrations.
No overdose data are available for horses.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable

3.12 Withdrawal period

Cattle and horses:
Meat and offal: Zero days.
Milk: Zero hours.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QA12CX99

4.2 Pharmacodynamic

Butafosfan is a synthetically produced organic phosphorus compound. It is used as an exogenous source of phosphorus, which is important for energy metabolism. It is essential for gluconeogenesis since most intermediates of that process need to be phosphorylated.

Cyanocobalamin is a unique cobalt-containing vitamin which is a semi-synthetic form of vitamin B12. It functions as a co-factor for two of the enzymes important in fatty acid synthesis and in the biosynthesis of glucose from propionate.
Cyanocobalamin belongs to the family of water-soluble B-vitamins which are synthesized by the microbial flora in the digestive tract of domestic animals (forestomachs and large intestine).
When administered parenterally, cyanocobalamin is directly available as a source of vitamin B12.

4.3 Pharmacokinetic

Butafosfan is rapidly absorbed from the injection site when administered subcutaneously or intramuscularly. The maximum plasma concentration is reached approximately 30 minutes after administration. Butafosfan is distributed to the liver, kidney, muscle and skin/fat and is excreted rapidly, mainly in urine (74 % in the first 12 hours), while less than 1 % is excreted in faeces.
In studies in cattle after a single intravenous administration of a single dose of 5 mg/kg body weight elimination is relatively rapid with a terminal half-life of 3.2 hours. In cows it was established that milk excretion was low.
In studies in horses, after intravenous administration of butafosfan at a dose of 10 mg/kg of body weight, the value C_{max} was reached within 1 minute, while the biological half-life is approximately 78 minutes.
In studies in dogs after a single subcutaneous administration of a single dose of 20 mg/kg body weight, absorption and butafosfan elimination is relatively rapid. T_{max} in dogs is 0.75 h, while the terminal half-life is approximately 9 hours.

Cyanocobalamin is rapidly and extensively absorbed into the blood after subcutaneous or intramuscular administration to animals. In serum, it is bound to specific transport proteins called transcobalamins. It is distributed extensively into all tissues and tends to accumulate in the liver. The principal routes of excretion of absorbed vitamin B_{12} are via urine, bile, and faeces. Urinary excretion of unmetabolised vitamin B_{12} by kidney glomerular filtration is minimal and biliary excretion via faeces is the major excretory route. Much of the cobalamin excreted in bile is reabsorbed; at least 65 to 75 % is reabsorbed in the ileum by means of the “intrinsic factor” active transport mechanism.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Store in the original packaging in order to protect from light.

5.4 Nature and composition of immediate packaging

Amber glass vials of glass type II with bromobutyl rubber stopper and aluminum overseal in a cardboard box.

Pack Sizes:
Cardboard box containing 1 vial of 50 ml solution for injection.
Cardboard box containing 1 vial of 100 ml solution for injection
Cardboard box containing 1 vial of 250 ml solution for injection

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Alivira Animal Health Limited

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorization:

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database. (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Butafosal 100 mg/ml + 0.05 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Butaphosphan	100 mg
Cyanocobalamin (Vitamin $_{B12}$)	0.05 mg

3. PACKAGE SIZE

50 ml
100 ml
250 ml

4. TARGET SPECIES

Cattle, horses and dogs.

5. INDICATION(S)

6. ROUTES OF ADMINISTRATION

Cattle and horses:

Intravenous use.

Dogs:

Intravenous, intramuscular and subcutaneous use.

7. WITHDRAWAL PERIOD

Withdrawal period:
Cattle and horses:
Meat and offal: Zero days.
Milk: Zero hours.

8. EXPIRY DATE

Exp.{mm/yyyy}

Once opened use within 28 days.
Once opened use by:

9. SPECIAL STORAGE PRECAUTIONS

This veterinary medicinal product does not require any special temperature storage conditions
Store in the original packaging in order to protect from light

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

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

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Alivira Animal Health Limited

14. MARKETING AUTHORISATION NUMBER(S)

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vial (100 ml, 250ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

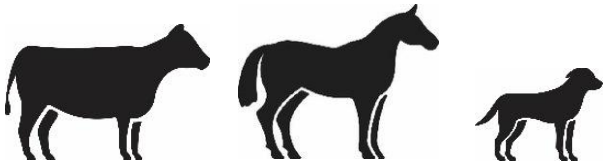
Butafosal 100 mg/ml + 0.05 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Butaphosphan	100 mg
Cyanocobalamin (Vitamin $_{B12}$)	0.05 mg

3. TARGET SPECIES



Cattle, horses and dogs.

4. ROUTES OF ADMINISTRATION

Cattle and horses:
Intravenous use.
Dogs:
Intravenous, intramuscular and subcutaneous use.

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
Cattle and horses:
Meat and offal: Zero days.
Milk: Zero hours.

6. EXPIRY DATE

Exp.{mm/yyyy}

Once opened use within 28 days.
Once opened use by:

7. SPECIAL STORAGE PRECAUTIONS

This veterinary medicinal product does not require any special temperature storage conditions.
Store in the original packaging in order to protect from light

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Alivira Animal Health Limited

9. BATCH NUMBER

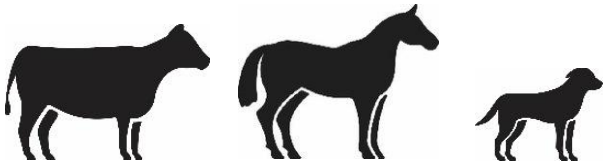
Lot{number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial (50 ml,)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Butafosal



2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Each ml contains:

Butaphosphan	100 mg
Cyanocobalamin (Vitamin $_{B12}$)	0.05 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once opened use within 28 days.
Once opened use by:

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

1. Name of the veterinary medicinal product

Butafosal 100 mg/ml + 0.05 mg/ml solution for injection for cattle, horses and dogs

2. Composition

Each ml contains:

Active substances:

Butaphosphan	100 mg
Cyanocobalamin (Vitamin $_{B12}$)	0.05 mg

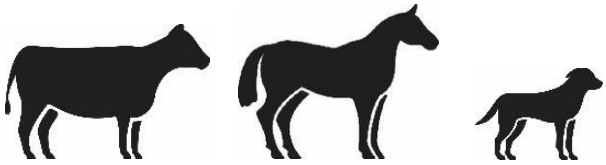
Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl Alcohol (E1519)	10.5 mg
Sodium Hydroxide (for pH adjustment)	-
Water for injection	-

Clear, pink to red coloured solution, free from visible particulate matter.

3. Target species

Cattle, horses and dogs.



4. Indications for use

All target species:
- Supportive treatment and prevention of hypophosphatemia and/or cyanocobalamin (vitamin B_{12}) deficiency.

Cattle:
- Supportive treatment to restore rumination following surgical treatment of displaced abomasum associated with secondary ketosis.
- Complementary treatment of parturient paresis in addition to Ca/Mg therapy.
- Prevention of ketosis development, if administered before calving.

Horses:
- Adjunctive therapy in horses suffering from muscular exhaustion.

5. Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.

6. Special warnings

Special warnings:

None.

Special precautions for safe use in the target species:

Intravenous administration should be done very slowly since cases of circulatory shock may be associated with too rapid injection.

In dogs suffering from chronic renal insufficiency the veterinary medicinal product should only be used according to the benefit-risk assessment by the responsible veterinarian.

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

Accidental self-injection of this veterinary medicinal product may cause adverse effects.
Self-injection should be avoided.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause skin and eye irritation.
Avoid contact with skin and eyes.
In case of accidental exposure, rinse the affected area thoroughly with water.

The active substance cyanocobalamin and the excipient benzyl alcohol may cause hypersensitivity reactions.
People with known hypersensitivity to these ingredients should avoid contact with the veterinary medicinal product.
If you develop symptoms following exposure, such as a skin rash, seek medical advice and show the package leaflet or the label to the physician.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation in mares and bitches.

Cows:
Can be used during pregnancy and lactation in cows.

Horses and dogs:
Laboratory studies in rats have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
Use only according to the benefit-risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:

None known.

Overdose:

No adverse effect was reported after intravenous administrations up to 5 times the recommended dose in cattle.

Except transient slight swelling at the injection site, no other adverse effect was reported after subcutaneous administrations up to 5 times the recommended dose in dogs.

No overdose data are available for dogs after intravenous and intramuscular administrations.

No overdose data are available for horses.

Major Incompatibilities:

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

7. Adverse events

Cattle, horses and dogs

Rare (1 to 10 animals / 10,000 animals treated):	- Injection site pain[1]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	- Circulatory shock[2]

[1]Has been reported following subcutaneous administration in dogs.

[2]In cases where rapid intravenous infusion has occurred.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holderusing the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

Cattle and horses:
Intravenous use.

Dogs:
Intravenous, intramuscular and subcutaneous use.

The dose depends on the animal's body weight (bw) and condition.

Species	Dose butafosfan (mg/kg bw)	Dose cyanocobalamin (mg/kg bw)	Dose volume of the veterinary medicinal product	Route of administration
Cattle Horses	5–10	0.0025-0.005	5–10 ml/100 kg	i.v.
Dogs	10–15	0.005–0.0075	0.1–0.15 ml/kg	i.v., i.m., s.c.

For the supportive treatment of secondary ketosis in cows, the recommended dose should be administered on three consecutive days.
For the prevention of ketosis in cows, the recommended dose should be administered on three consecutive days within the period of 10 days before expected calving.

For other indications, treatment should be repeated as necessary.

To ensure a correct dosage, body weight should be determined as accurately as possible.

The rubber stopper of the vial may be safely punctured up to 40 times with 18 gauge needle. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used to avoid excessive puncturing of the closure.

9. Advise on correct administration

It is recommended that the solution is warmed to body temperature before administration.

The rubber stopper of the vial may be safely punctured up to 40 times with 18 gauge needle. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used to avoid excessive puncturing of the closure.

10. Withdrawal periods

Cattle and horses:
Meat and offal: Zero days.
Milk: Zero hours.

11. Special storage precautions

Keep out of the sight and reach of children

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

Store in the original packaging in order to protect from light.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Shelf life after first opening the immediate packaging: 28 days

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems . These measures should help to protect the environment.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Amber glass vials of glass type II with bromobutyl rubber stopper and aluminum overseal in a cardboard box.

Cardboard box containing 1 vial of 50 ml solution for injection.
Cardboard box containing 1 vial of 100 ml solution for injection.
Cardboard box containing 1 vial of 250 ml solution for injection.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

MM/YYYY

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary)

16. Contact details

Marketing authorisation holder

Alivira Animal Health Limited
2ndFloor, 1-2 Victoria Buildings,
Haddington Road, Dublin 4,
004 XN32, Ireland

Manufacturer responsible for batch release:

LABORATORIOS KARIZOO S.A
Mas Pujades 11-12, Polígono Industrial La Borda,

08140 Caldes de Montbui, Spain

Contact details to report suspected adverse events:
For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

17. Other information