

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml suspension for injection for cats and dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Insulin human* 40 IU as protamine zinc insulin.

One IU (International Unit) corresponds to 0.0347 mg of insulin human.

*produced by recombinant DNA technology

Excipients:

Protamine sulfate	0.466 mg
Zinc oxide	0.088 mg
Phenol	2.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Cloudy, white, aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cats and dogs

4.2 Indications for use, specifying the target species

For the treatment of diabetes mellitus in cats and dogs to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

4.3 Contraindications

Do not use for the acute management of diabetic ketoacidosis.

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

4.4 Special warnings for each target species

Very stressful events, inappetance, concomitant treatment with gestagens and corticosteroids or other concomitant diseases (e.g. gastro-intestinal, infectious or inflammatory or endocrine diseases), might influence insulin effectiveness and therefore the insulin dose may need to be adjusted.

4.5 Special precautions for use

Special precautions for use in animals

The insulin dose may need to be adjusted or discontinued in case of remission of the diabetic state in cats or

after resolution of transient diabetic stages in dogs (e.g. dioestrus-induced diabetes mellitus, diabetes mellitus secondary to hyperadrenocorticism).

After the daily insulin dose is established, monitoring for diabetic control is recommended. Treatment with insulin can cause hypoglycaemia, for clinical signs and appropriate treatment, see section 4.10.

Special precautions for use in dogs

In cases where hypoglycaemia is suspected, blood glucose measurements should be taken at the time of occurrence (if possible) as well as shortly prior to the next feeding/injection (where applicable). Stress and irregular exercise should be avoided. It is recommended to establish a regular twice daily feeding schedule with the owner whether injecting insulin once or twice daily.

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

Accidental self-injection can provoke clinical signs of hypoglycaemia which may be treated by oral administration of sugar. There is a low possibility of an allergic reaction in sensitised individuals.

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

4.6 Adverse reactions (frequency and seriousness)

Hypoglycaemic reactions were very commonly reported in clinical studies: 13% (23 of 176) of treated cats and 26.5% (44 of 166) of treated dogs. These reactions were generally mild in nature. Clinical signs may include hunger, anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation.

In this case immediate administration of a glucose containing solution or gel and/or food is required.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

Local injection site reactions were very rarely reported and resolved without cessation of therapy.

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

- very common (more than 1 in 10 animals treated displaying adverse reactions)
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety and efficacy of ProZinc in breeding, pregnant and lactating animals has not been evaluated.

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

In general, insulin requirements during pregnancy and lactation might be different due to a change in the metabolic state. Therefore, close glucose monitoring and veterinary supervision is advised.

4.8 Interaction with other medicinal products and other forms of interaction

Changes in insulin requirements may result from administration of substances which alter glucose tolerance (e.g. corticosteroids and gestagens). Monitoring of glucose concentrations should be performed to adjust the dose accordingly. Similarly, feeding cats with a high protein/low carbohydrate diet and changing the diet of any given cat or dog may alter insulin requirements and necessitate a change of insulin dose.

4.9 Amounts to be administered and administration route

Subcutaneous use.

If the animal owner is to administer the product, suitable training/advice should be provided by the prescribing veterinarian before using for the first time.

Dosage:

The veterinarian should re-evaluate the animal at appropriate intervals and make adjustments to the treatment protocol, for instance dose and dosing regimen, until adequate glycaemic control has been attained.

Any dose adjustment (i.e. increase of dose) should be in general performed after several days (e.g. 1 week) since full action of insulin requires an equilibration phase. Dose reductions due to observed hypoglycaemia or suspected Somogyi effect (rebound hyperglycaemia) may be of 50% or higher (potentially including a temporary pause of insulin administration).

Once adequate glycaemic control is achieved intermittent glucose monitoring should be performed, especially when there is a change in clinical signs or diabetic remission is suspected, and further adjustments in the insulin dose might be necessary.

Cats:

The initial recommended dose is 0.2 to 0.4 IU insulin/kg bodyweight every 12 hours.

- For cats previously controlled on insulin, a higher starting dose up to 0.7 IU insulin/kg bodyweight may be appropriate.
- Adjustments of insulin dose if required should usually be done between 0.5 to 1 IU insulin per injection.

Cats can develop diabetic remission, in which case sufficient endogenous insulin production will be regained and exogenous insulin dose will need to be adjusted or ceased.

Dogs:

General guidance:

Dosing should be individualised and based on the clinical presentation of each patient. To achieve optimal control of diabetes mellitus, dose adjustments should primarily be based on clinical signs. Blood parameters such as fructosamine, maximum blood glucose and decrease of blood glucose concentrations in blood glucose curves conducted over a sufficient period of time to determine a blood glucose nadir should be used as supporting tools.

Re-evaluation of clinical signs and laboratory parameters should be performed as recommended by the attending veterinarian.

Initiation

For initiation of treatment, the recommended dose is 0.5 to 1.0 IU insulin/kg bodyweight once daily every morning (approx. every 24 h).

For newly diagnosed diabetic dogs, a starting dose of 0.5 IU insulin/kg once daily is recommended.

Management

Adjustments of insulin dose on a once daily regimen, if required, should generally be done in a conservative and gradual manner, (e.g. up to 25% increase/decrease of the dose per injection).

If insufficient improvement in diabetic control is observed after an adequate dose adjustment period of 4 to 6 weeks on once daily treatment, the following options may be considered:

- Further adjustments of insulin dose on once daily treatment may be necessary; in particular if dogs undertake increased physical activity, have a change of their usual diet or during concomitant illness.
- Switching to twice daily dosing: In such cases, it is recommended to reduce the dose per injection by one third (e.g. 12 kg dog being treated once daily with 12 IU insulin/injection may be switched to 8 IU

insulin/injection administered twice daily). The product should be administered in the morning and in the evening, approx. 12 hours apart. Further adjustments of insulin dose on twice daily treatment may be necessary.

Depending on the underlying cause (e.g. dioestrus-induced diabetes mellitus), dogs can develop diabetic remission, although more seldom than in cats. In those cases sufficient endogenous insulin production will be regained and the exogenous insulin dose will need to be adjusted or ceased.

Method of administration:

A U-40 syringe must be used.

The suspension should be mixed by gently rolling the vial prior to withdrawing each dose from the vial.

The dose should be given concurrently with or immediately after a meal.

Particular care should be taken with regard to the accuracy of dosing.

The veterinary medicinal product should be administered by subcutaneous injection.

Avoid introduction of contamination during use.

After gently rolling the vial, ProZinc suspension has a white, cloudy appearance.

A white ring may be seen in the neck of some vials, but this does not affect the quality of the product.

Agglomerates (e.g. clumps) can form in insulin suspensions: do not use the product if visible agglomerates persist after gently rolling the vial.

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

An overdose of insulin can result in hypoglycaemia in which case immediate administration of a glucose containing solution or gel and/or food is required.

Clinical signs may include hunger, increasing anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

The owner is advised to have glucose containing products (e.g. honey, dextrose gel) in the household.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Insulins and analogues for injection, intermediate acting.

ATCvet code: QA10AC01 Insulin (human).

5.1 Pharmacodynamic properties

Insulin activates insulin receptors and therewith a complex cell signaling cascade which results in increased glucose uptake into the cells. The main effects of insulin are the reduction in circulating blood glucose concentrations and the storage of fat. Overall insulin influences the regulation of the carbohydrate and fat metabolism.

Under clinical field conditions in diabetic cats the maximal action on blood glucose concentrations (e.g. blood glucose nadir) after subcutaneous administration was observed at a mean of 6 hours (range 3 to 9 hours). In the majority of cats the glucose lowering effect lasted for a minimum of 9 hours after first insulin injection.

In an experimental study in healthy dogs, the time to blood glucose nadir after a single subcutaneous injection of 0.8 or 0.5 IU/kg bodyweight of the product was variable between dogs (range 3 to >24 hours), as was the duration of insulin action (range 12 to >24 hours). Median time to blood glucose nadir was

approximately 16 and 12 hours following administration of 0.5 or 0.8 IU/kg bodyweight, respectively. Under clinical field conditions in diabetic dogs, time to maximal effect in lowering blood glucose concentrations (i.e. blood glucose nadir) after subcutaneous administration was not observed within 9 hours after last injection in 67.9% of dogs overall. (73.5% on once daily and 59.3% on twice daily administration). Consequently, blood glucose curves should be conducted over a sufficient period to determine a blood glucose nadir.

5.2 Pharmacokinetic particulars

Absorption:

Protamine zinc recombinant human insulin is an insulin whose absorption and onset of action is delayed by the addition of protamine and zinc leading to crystal formation. After subcutaneous injection, proteolytic tissue enzymes degrade protamine to permit the absorption of insulin. In addition, interstitial fluid will dilute and break down the formed zinc insulin hexamer complexes and result in a delayed absorption from the subcutaneous depot.

Distribution:

Once absorbed from the subcutaneous site, insulin will enter the circulation and diffuse into tissues, where it binds to insulin receptors found on most tissues. Target tissue organs are i.e. liver, muscle and adipose tissue.

Metabolism:

Following the binding of insulin with the insulin receptor and the subsequent action, insulin is released back into the extracellular environment. It may then be degraded on passage through the liver or by the kidney. Degradation normally involves endocytosis of the insulin-receptor complex, followed by the action of insulin-degrading enzyme.

Elimination:

The liver and the kidney are the two main organs which eliminate insulin from the circulation. Forty per cent of insulin is eliminated by the liver and 60% is eliminated by the kidney.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulfate
Zinc oxide
Glycerol
Dibasic sodium phosphate, heptahydrate
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this product must 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: 60 days.

6.4 Special precautions for storage

For unused and broached vials:

Store upright in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Pack size of one clear glass vial of 10 ml.

The vial is closed with a butyl rubber stopper and sealed with a plastic flip-off cap.

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Vetmedica GmbH
Binger Strasse 173
55216 Ingelheim/Rhein
GERMANY

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/152/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12/07/2013

Date of last renewal: 13/04/2018

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.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml suspension for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Insulin human* 40 IU as protamine zinc insulin.

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*produced by recombinant DNA technology

Excipients:

Protamine sulfate	0.466 mg
Zinc oxide	0.088 mg
Phenol	2.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Cloudy, white, aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

For the treatment of diabetes mellitus in dogs to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

4.3 Contraindications

Do not use for the acute management of diabetic ketoacidosis.

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

4.4 Special warnings for each target species

Very stressful events, inappetance, concomitant treatment with gestagens and corticosteroids or other concomitant diseases (e.g. gastro-intestinal, infectious or inflammatory or endocrine diseases), might influence insulin effectiveness and therefore the insulin dose may need to be adjusted.

4.5 Special precautions for use

Special precautions for use in animals

The insulin dose may need to be adjusted or discontinued after resolution of transient diabetic stages (e.g.

dioestrus-induced diabetes mellitus, diabetes mellitus secondary to hyperadrenocorticism).

After the daily insulin dose is established, monitoring for diabetic control is recommended. Treatment with insulin can cause hypoglycaemia, for clinical signs and appropriate treatment, see section 4.10.

In cases where hypoglycaemia is suspected, blood glucose measurements should be taken at the time of occurrence (if possible) as well as shortly prior to the next feeding/injection (where applicable). Stress and irregular exercise should be avoided. It is recommended to establish a regular twice daily feeding schedule with the owner whether injecting insulin once or twice daily.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Accidental self-injection can provoke clinical signs of hypoglycaemia which may be treated by oral administration of sugar. There is a low possibility of an allergic reaction in sensitised individuals.

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

4.6 Adverse reactions (frequency and seriousness)

Hypoglycaemic reactions were very commonly reported in a clinical study: 26.5% (44 of 166) of treated dogs. These reactions were generally mild in nature. Clinical signs may include hunger, anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation. In this case immediate administration of a glucose containing solution or gel and/or food is required.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

Local injection site reactions were very rarely reported and resolved without cessation of therapy.

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

- very common (more than 1 in 10 animals treated displaying adverse reactions)
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety and efficacy of ProZinc in breeding, pregnant and lactating animals has not been evaluated.

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

In general, insulin requirements during pregnancy and lactation might be different due to a change in the metabolic state. Therefore, close glucose monitoring and veterinary supervision is advised.

4.8 Interaction with other medicinal products and other forms of interaction

Changes in insulin requirements may result from administration of substances which alter glucose tolerance (e.g. corticosteroids and gestagens). Monitoring of glucose concentrations should be performed to adjust the dose accordingly. Similarly, changing the diet may alter insulin requirements and necessitate a change of insulin dose.

4.9 Amounts to be administered and administration route

Subcutaneous use.

If the animal owner is to administer the product, suitable training/advice should be provided by the prescribing veterinarian before using for the first time.

Dosage:

The veterinarian should re-evaluate the animal at appropriate intervals and make adjustments to the treatment protocol, for instance dose and dosing regimen, until adequate glycaemic control has been attained.

Any dose adjustment (i.e. increase of dose) should be in general performed after several days (e.g. 1 week) since full action of insulin requires an equilibration phase. Dose reductions due to observed hypoglycaemia or suspected Somogyi effect (rebound hyperglycaemia) may be of 50% or higher (potentially including a temporary pause of insulin administration).

Once adequate glycaemic control is achieved intermittent glucose monitoring should be performed, especially when there is a change in clinical signs, and further adjustments in the insulin dose might be necessary.

General guidance:

Dosing should be individualised and based on the clinical presentation of each patient. To achieve optimal control of diabetes mellitus, dose adjustments should primarily be based on clinical signs. Blood parameters such as fructosamine, maximum blood glucose and decrease of blood glucose concentrations in blood glucose curves conducted over a sufficient period of time to determine a blood glucose nadir should be used as supporting tools.

Re-evaluation of clinical signs and laboratory parameters should be performed as recommended by the attending veterinarian.

Initiation

For initiation of treatment, the recommended dose is 0.5 to 1.0 IU insulin/kg bodyweight once daily every morning (approx. every 24 h).

For newly diagnosed diabetic dogs, a starting dose of 0.5 IU insulin/kg once daily is recommended.

Management

Adjustments of insulin dose on a once daily regimen, if required, should generally be done in a conservative and gradual manner, (e.g. up to 25% increase/decrease of the dose per injection).

If insufficient improvement in diabetic control is observed after an adequate dose adjustment period of 4 to 6 weeks on once daily treatment, the following options may be considered:

- Further adjustments of insulin dose on once daily treatment may be necessary; in particular if dogs undertake increased physical activity, have a change of their usual diet or during concomitant illness.
- Switching to twice daily dosing: In such cases, it is recommended to reduce the dose per injection by one third (e.g. 12 kg dog being treated once daily with 12 IU insulin/injection may be switched to 8 IU insulin/injection administered twice daily). The product should be administered in the morning and in the evening, approx. 12 hours apart. Further adjustments of insulin dose on twice daily treatment may be necessary.

Depending on the underlying cause (e.g. dioestrus-induced diabetes mellitus), dogs can develop diabetic remission, although seldom. In those cases sufficient endogenous insulin production will be regained and the exogenous insulin dose will need to be adjusted or ceased.

Method of administration:

A U-40 syringe must be used.

The suspension should be mixed by gently rolling the vial prior to withdrawing each dose from the vial.

The dose should be given concurrently with or immediately after a meal.

Particular care should be taken with regard to the accuracy of dosing.

The veterinary medicinal product should be administered by subcutaneous injection.

Avoid introduction of contamination during use.

After gently rolling the vial, ProZinc suspension has a white, cloudy appearance. A white ring may be seen in the neck of some vials, but this does not affect the quality of the product. Agglomerates (e.g. clumps) can form in insulin suspensions: do not use the product if visible agglomerates persist after gently rolling the vial.

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

An overdose of insulin can result in hypoglycaemia in which case immediate administration of a glucose containing solution or gel and/or food is required.

Clinical signs may include hunger, increasing anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately. The owner is advised to have glucose containing products (e.g. honey, dextrose gel) in the household.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Insulins and analogues for injection, intermediate acting.
ATCvet code: QA10AC01 Insulin (human).

5.1 Pharmacodynamic properties

Insulin activates insulin receptors and therewith a complex cell signaling cascade which results in increased glucose uptake into the cells. The main effects of insulin are the reduction in circulating blood glucose concentrations and the storage of fat. Overall insulin influences the regulation of the carbohydrate and fat metabolism.

In an experimental study in healthy dogs, the time to blood glucose nadir after a single subcutaneous injection of 0.8 or 0.5 IU/kg bodyweight of the product was variable between dogs (range 3 to >24 hours), as was the duration of insulin action (range 12 to >24 hours). Median time to blood glucose nadir was approximately 16 and 12 hours following administration of 0.5 or 0.8 IU/kg bodyweight, respectively.

Under clinical field conditions in diabetic dogs, time to maximal effect in lowering blood glucose concentrations (i.e. blood glucose nadir) after subcutaneous administration was not observed within 9 hours after last injection in 67.9% of dogs overall. (73.5% on once daily and 59.3% on twice daily administration). Consequently, blood glucose curves should be conducted over a sufficient period to determine a blood glucose nadir.

5.2 Pharmacokinetic particulars

Absorption:

Protamine zinc recombinant human insulin is an insulin whose absorption and onset of action is delayed by the addition of protamine and zinc leading to crystal formation. After subcutaneous injection, proteolytic tissue enzymes degrade protamine to permit the absorption of insulin. In addition, interstitial fluid will dilute and break down the formed zinc insulin hexamer complexes and result in a delayed absorption from the subcutaneous depot.

Distribution:

Once absorbed from the subcutaneous site, insulin will enter the circulation and diffuse into tissues, where it binds to insulin receptors found on most tissues. Target tissue organs are i.e. liver, muscle and adipose tissue.

Metabolism:

Following the binding of insulin with the insulin receptor and the subsequent action, insulin is released back into the extracellular environment. It may then be degraded on passage through the liver or by the kidney. Degradation normally involves endocytosis of the insulin-receptor complex, followed by the action of insulin-degrading enzyme.

Elimination:

The liver and the kidney are the two main organs which eliminate insulin from the circulation. Forty per cent of insulin is eliminated by the liver and 60% is eliminated by the kidney.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulfate
Zinc oxide
Glycerol
Dibasic sodium phosphate, heptahydrate
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this product must 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: 60 days.

6.4 Special precautions for storage

For unused and broached vials:
Store upright in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Pack size of one clear glass vial of 20 ml.
The vial is closed with a butyl rubber stopper and sealed with a plastic flip-off cap.

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Vetmedica GmbH
Binger Strasse 173
55216 Ingelheim/Rhein
GERMANY

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/152/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12/07/2013
Date of last renewal: 13/04/2018

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 manufacturers responsible for batch release

Boehringer Ingelheim Vetmedica GmbH
Binger Strasse 173
55216 Ingelheim/Rhein
GERMANY

KVP Pharma + Veterinär Produkte GmbH
Projensdorfer Str. 324
24106 Kiel
GERMANY

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Specific pharmacovigilance requirements:

Amendment of the periodic safety update report (PSUR) cycle is required, as detailed in the CVMP assessment report.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE**Carton for 10 ml****1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

ProZinc 40 IU/ml suspension for injection for cats and dogs
insulin human as protamine zinc insulin

2. STATEMENT OF ACTIVE SUBSTANCES

40 IU/ml of insulin human

3. PHARMACEUTICAL FORM

Suspension for injection

4. PACKAGE SIZE

1 x 10 ml

5. TARGET SPECIES

Cats and dogs

6. INDICATION(S)**7. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)**9. SPECIAL WARNING(S), IF NECESSARY****10. EXPIRY DATE**

EXP {month/year}

Once broached use within 60 days.

11. SPECIAL STORAGE CONDITIONS

Store upright in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

12. SPECIFIC PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Disposal: read 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

Boehringer Ingelheim Vetmedica GmbH
55216 Ingelheim/Rhein
GERMANY

16. MARKETING AUTHORISATION NUMBERS

EU/2/13/152/001

17. MANUFACTURER’S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial, 10 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml injection for cats and dogs
insulin human as protamine zinc insulin

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

40 IU/ml

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

10 ml

4. ROUTE(S) OF ADMINISTRATION

SC

5. WITHDRAWAL PERIOD(S)**6. BATCH NUMBER**

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once broached use by ...

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton for 20 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml suspension for injection for dogs
insulin human as protamine zinc insulin

2. STATEMENT OF ACTIVE SUBSTANCES

40 IU/ml of insulin human

3. PHARMACEUTICAL FORM

Suspension for injection

4. PACKAGE SIZE

1 x 20 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)**7. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)**9. SPECIAL WARNING(S), IF NECESSARY****10. EXPIRY DATE**

EXP {month/year}

Once broached use within 60 days.

11. SPECIAL STORAGE CONDITIONS

Store upright in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

12. SPECIFIC PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Disposal: read 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

Boehringer Ingelheim Vetmedica GmbH
55216 Ingelheim/Rhein
GERMANY

16. MARKETING AUTHORISATION NUMBERS

EU/2/13/152/002

17. MANUFACTURER’S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial, 20 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml injection for dogs
insulin human as protamine zinc insulin

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

40 IU/ml

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

20 ml

4. ROUTE(S) OF ADMINISTRATION

SC

5. WITHDRAWAL PERIOD(S)**6. BATCH NUMBER**

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once broached use by ...

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
ProZinc 40 IU/ml suspension for injection for cats and dogs

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

Marketing authorisation holder and manufacturer responsible for batch release:

Boehringer Ingelheim Vetmedica GmbH
Binger Strasse 173
55216 Ingelheim/Rhein
GERMANY

Manufacturer responsible for batch release:

KVP Pharma + Veterinär Produkte GmbH
Projensdorfer Str. 324
24106 Kiel
GERMANY

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml suspension for injection for cats and dogs
insulin human

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENTS

Each ml contains:

Active substance:

Insulin human* 40 IU as protamine zinc insulin.

One IU (International Unit) corresponds to 0.0347 mg of insulin human.

*produced by recombinant DNA technology

Excipients:

Protamine sulfate	0.466 mg
Zinc oxide	0.088 mg
Phenol	2.5 mg

Cloudy, white, aqueous suspension.

4. INDICATION(S)

For the treatment of diabetes mellitus in cats and dogs to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

5. CONTRAINDICATIONS

Do not use for the acute management of diabetic ketoacidosis.

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

6. ADVERSE REACTIONS

Hypoglycaemic reactions were very commonly reported in clinical studies: 13% (23 of 176) of treated cats and 26.5% (44 of 166) of treated dogs. These reactions were generally mild in nature. Clinical signs may include hunger, anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation.

In this case immediate administration of a glucose containing solution or gel and/or food is required.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

Local injection site reactions were very rarely reported and resolved without cessation of therapy.

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

- very common (more than 1 in 10 animals treated displaying adverse reactions)
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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 inform your veterinary surgeon.

7. TARGET SPECIES

Cats and dogs

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

Subcutaneous use.

If the animal owner is to administer the product, suitable training/advice should be provided by the prescribing veterinarian before using for the first time.

Dosage:

The veterinarian should re-evaluate the animal at appropriate intervals and make adjustments to the treatment protocol, for instance dose and dosing regimen, until adequate glycaemic control has been attained.

Any dose adjustment (i.e. increase of dose) should be in general performed after several days (e.g. 1 week) since full action of insulin requires an equilibration phase. Dose reductions due to observed hypoglycaemia or suspected Somogyi effect (rebound hyperglycaemia) may be of 50% or higher (potentially including a temporary pause of insulin administration).

Once adequate glycaemic control is achieved intermittent glucose monitoring should be performed, especially when there is a change in clinical signs or diabetic remission is suspected, and further adjustments in the insulin dose might be necessary.

Cats:

The initial recommended dose is 0.2 to 0.4 IU insulin/kg bodyweight every 12 hours.

- For cats previously controlled on insulin, a higher starting dose up to 0.7 IU insulin/kg bodyweight may be appropriate.
- Adjustments of insulin dose if required should usually be done between 0.5 to 1 IU insulin per injection.

Cats can develop diabetic remission, in which case sufficient endogenous insulin production will be regained and exogenous insulin dose will need to be adjusted or ceased.

Dogs:

General guidance:

Dosing should be individualised and based on the clinical presentation of each patient. To achieve optimal control of diabetes mellitus, dose adjustments should primarily be based on clinical signs. Blood parameters such as fructosamine, maximum blood glucose and decrease of blood glucose concentrations in blood glucose curves conducted over a sufficient period of time to determine a blood glucose nadir should be used as supporting tools (see also section “Special precautions for use in dogs”).

Re-evaluation of clinical signs and laboratory parameters should be performed as recommended by the attending veterinarian.

Initiation

For initiation of treatment, the recommended dose is 0.5 to 1.0 IU insulin/kg bodyweight once daily every morning (approx. every 24 h).

For newly diagnosed diabetic dogs, a starting dose of 0.5 IU insulin/kg once daily is recommended.

Management

Adjustments of insulin dose on a once daily regimen, if required, should generally be done in a conservative and gradual manner, (e.g. up to 25% increase/decrease of the dose per injection).

If insufficient improvement in diabetic control is observed after an adequate dose adjustment period of 4 to 6 weeks on once daily treatment, the following options may be considered:

- Further adjustments of insulin dose on once daily treatment may be necessary; in particular if dogs undertake increased physical activity, have a change of their usual diet or during concomitant illness.
- Switching to twice daily dosing: In such cases, it is recommended to reduce the dose per injection by one third (e.g. 12 kg dog being treated once daily with 12 IU insulin/injection may be switched to 8 IU insulin/injection administered twice daily). The product should be administered in the morning and in the evening, approx. 12 hours apart. Further adjustments of insulin dose on twice daily treatment may be necessary.

Depending on the underlying cause (e.g. dioestrus-induced diabetes mellitus), dogs can develop diabetic remission, although more seldom than in cats. In those cases sufficient endogenous insulin production will be regained and the exogenous insulin dose will need to be adjusted or ceased.

9. ADVICE ON CORRECT ADMINISTRATION

A U-40 syringe must be used.

The suspension should be mixed by gently rolling the vial prior to withdrawing each dose from the vial.

Particular care should be taken with regard to the accuracy of dosing.

The veterinary medicinal product should be administered by subcutaneous injection.

The dose should be given concurrently with or immediately after a meal.

Avoid introduction of contamination during use.

After gently rolling the vial, ProZinc suspension has a white, cloudy appearance.

A white ring may be seen in the neck of some vials, but this does not affect the quality of the product.

Agglomerates (e.g. clumps) can form in insulin suspensions: do not use the product if visible agglomerates persist after gently rolling the vial.

10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

For unused and broached vials:

Store upright in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Shelf life after first opening the container: 60 days.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton and the vial after EXP.

12. SPECIAL WARNING(S)

Special warnings for each target species:

Very stressful events, inappetance, concomitant treatment with gestagens and corticosteroids or other concomitant diseases (e.g. gastro-intestinal, infectious or inflammatory or endocrine diseases), might influence insulin effectiveness and therefore the insulin dose may need to be adjusted.

Special precautions for use in animals:

The insulin dose may need to be adjusted or discontinued in case of remission of the diabetic state in cats or after resolution of transient diabetic stages in dogs (e.g. dioestrus-induced diabetes mellitus, diabetes mellitus secondary to hyperadrenocorticism).

After the daily insulin dose is established, monitoring for diabetic control is recommended.

Treatment with insulin can cause hypoglycaemia, for clinical signs and appropriate treatment, please refer to section “Overdose”, below.

Special precautions for use in dogs

In cases where hypoglycaemia is suspected, blood glucose measurements should be taken at the time of occurrence (if possible) as well as shortly prior to the next feeding/injection (where applicable).

Stress and irregular exercise should be avoided. It is recommended to establish a regular twice daily feeding schedule with the owner whether injecting insulin once or twice daily.

In an experimental study in healthy dogs, median time to blood glucose nadir was approximately 16 and 12 hours following administration of 0.5 or 0.8 IU/kg bodyweight, respectively.

Under clinical field conditions in diabetic dogs, time to maximal effect in lowering blood glucose concentrations (i.e. blood glucose nadir) after subcutaneous administration was not observed within 9 hours after last injection in 67.9% of dogs overall. (73.5% on once daily and 59.3% on twice daily administration). Consequently, blood glucose curves should be conducted over a sufficient period to determine a blood glucose nadir.

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

Accidental self-injection can provoke clinical signs of hypoglycaemia which may be treated by oral administration of sugar. There is a low possibility of an allergic reaction in sensitised individuals.

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

Pregnancy and lactation:

The safety and efficacy of ProZinc in breeding, pregnant and lactating animals has not been evaluated.

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

In general, insulin requirements during pregnancy and lactation might be different due to a change in the metabolic state. Therefore, close glucose monitoring and veterinary supervision is advised.

Interaction with other medicinal products and other forms of interaction:

Changes in insulin requirements may result from administration of substances which alter glucose tolerance (e.g. corticosteroids and gestagens). Monitoring of glucose concentrations should be performed to adjust the dose accordingly. Similarly, feeding cats with a high protein/low carbohydrate diet and changing the diet of any given cat or dog may alter insulin requirements and necessitate a change of insulin dose.

Overdose (symptoms, emergency procedures, antidotes):

An overdose of insulin can result in hypoglycaemia in which case immediate administration of a glucose containing solution or gel and/or food is required.

Clinical signs may include hunger, increasing anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

The owner is advised to have glucose containing products (e.g. honey, dextrose gel) in the household.

Major incompatibilities:

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

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

Medicines should not be disposed via wastewater or household waste. 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

Pack size of 1 clear glass vial of 10 ml. The vial is closed with a butyl rubber stopper and sealed with a plastic flip-off cap.

PACKAGE LEAFLET:
ProZinc 40 IU/ml suspension for injection for dogs

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

Marketing authorisation holder and manufacturer responsible for batch release:

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2. NAME OF THE VETERINARY MEDICINAL PRODUCT

ProZinc 40 IU/ml suspension for injection for dogs
insulin human

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENTS

Each ml contains:

Active substance:

Insulin human* 40 IU as protamine zinc insulin.

One IU (International Unit) corresponds to 0.0347 mg of insulin human.

*produced by recombinant DNA technology

Excipients:

Protamine sulfate	0.466 mg
Zinc oxide	0.088 mg
Phenol	2.5 mg

Cloudy, white, aqueous suspension.

4. INDICATION(S)

For the treatment of diabetes mellitus in dogs to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

5. CONTRAINDICATIONS

Do not use for the acute management of diabetic ketoacidosis.

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

6. ADVERSE REACTIONS

Hypoglycaemic reactions were very commonly reported in a clinical study: 26.5% (44 of 166) of treated dogs. These reactions were generally mild in nature. Clinical signs may include hunger, anxiety, unstable locomotion, muscle twitching, stumbling or sinking in the rear legs and disorientation.

In this case immediate administration of a glucose containing solution or gel and/or food is required.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

Local injection site reactions were very rarely reported and resolved without cessation of therapy.

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

- very common (more than 1 in 10 animals treated displaying adverse reactions)
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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 inform your veterinary surgeon.

7. TARGET SPECIES

Dogs

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

Subcutaneous use.

If the animal owner is to administer the product, suitable training/advice should be provided by the prescribing veterinarian before using for the first time.

Dosage:

The veterinarian should re-evaluate the animal at appropriate intervals and make adjustments to the treatment protocol, for instance dose and dosing regimen, until adequate glycaemic control has been attained.

Any dose adjustment (i.e. increase of dose) should be in general performed after several days (e.g. 1 week) since full action of insulin requires an equilibration phase. Dose reductions due to observed hypoglycaemia or suspected Somogyi effect (rebound hyperglycaemia) may be of 50% or higher (potentially including a temporary pause of insulin administration).

Once adequate glycaemic control is achieved intermittent glucose monitoring should be performed, especially when there is a change in clinical signs, and further adjustments in the insulin dose might be necessary.

General guidance:

Dosing should be individualised and based on the clinical presentation of each patient. To achieve optimal control of diabetes mellitus, dose adjustments should primarily be based on clinical signs. Blood parameters such as fructosamine, maximum blood glucose and decrease of blood glucose concentrations in blood glucose curves conducted over a sufficient period of time to determine a blood glucose nadir should be used as supporting tools (see also section “Special precautions for use in animals”).

Re-evaluation of clinical signs and laboratory parameters should be performed as recommended by the

attending veterinarian.

Initiation

For initiation of treatment, the recommended dose is 0.5 to 1.0 IU insulin/kg bodyweight once daily every morning (approx. every 24 h).

For newly diagnosed diabetic dogs, a starting dose of 0.5 IU insulin/kg once daily is recommended.

Management

Adjustments of insulin dose on a once daily regimen, if required, should generally be done in a conservative and gradual manner, (e.g. up to 25% increase/decrease of the dose per injection).

If insufficient improvement in diabetic control is observed after an adequate dose adjustment period of 4 to 6 weeks on once daily treatment, the following options may be considered:

- Further adjustments of insulin dose on once daily treatment may be necessary; in particular if dogs undertake increased physical activity, have a change of their usual diet or during concomitant illness.
- Switching to twice daily dosing: In such cases, it is recommended to reduce the dose per injection by one third (e.g. 12 kg dog being treated once daily with 12 IU insulin/injection may be switched to 8 IU insulin/injection administered twice daily). The product should be administered in the morning and in the evening, approx. 12 hours apart. Further adjustments of insulin dose on twice daily treatment may be necessary.

Depending on the underlying cause (e.g. dioestrus-induced diabetes mellitus), dogs can develop diabetic remission, although seldom. In those cases sufficient endogenous insulin production will be regained and the exogenous insulin dose will need to be adjusted or ceased.

9. ADVICE ON CORRECT ADMINISTRATION

A U-40 syringe must be used.

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10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

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For unused and broached vials:

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Do not freeze.

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after EXP.

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Special warnings for each target species:

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Special precautions for use in animals:

The insulin dose may need to be adjusted or discontinued after resolution of transient diabetic stages (e.g. dioestrus-induced diabetes mellitus, diabetes mellitus secondary to hyperadrenocorticism).

After the daily insulin dose is established, monitoring for diabetic control is recommended.

Treatment with insulin can cause hypoglycaemia, for clinical signs and appropriate treatment, please refer to section “Overdose”, below.

In cases where hypoglycaemia is suspected, blood glucose measurements should be taken at the time of occurrence (if possible) as well as shortly prior to the next feeding/injection (where applicable). Stress and irregular exercise should be avoided. It is recommended to establish a regular twice daily feeding schedule with the owner whether injecting insulin once or twice daily.

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Pregnancy and lactation:

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

In general, insulin requirements during pregnancy and lactation might be different due to a change in the metabolic state. Therefore, close glucose monitoring and veterinary supervision is advised.

Interaction with other medicinal products and other forms of interaction:

Changes in insulin requirements may result from administration of substances which alter glucose tolerance (e.g. corticosteroids and gestagens). Monitoring of glucose concentrations should be performed to adjust the dose accordingly. Similarly, changing the diet may alter insulin requirements and necessitate a change of insulin dose.

Overdose (symptoms, emergency procedures, antidotes):

An overdose of insulin can result in hypoglycaemia in which case immediate administration of a glucose containing solution or gel and/or food is required.

Clinical signs may include hunger, increasing anxiety, unstable locomotion, muscle twitching, stumbling or

sinking in the rear legs and disorientation.

Insulin administration should be temporarily stopped and the next dose of insulin adjusted appropriately.

The owner is advised to have glucose containing products (e.g. honey, dextrose gel) in the household.

Major incompatibilities:

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

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15. OTHER INFORMATION

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