

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 80 mg feline and bunny Spot-on solution [UK]

Advantage 80 mg Spot-on solution for Large Cats and Large Pet Rabbits [AT, DE, FR, IE, IT]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pipette of 0.8 ml contains:

Active substance:

Imidacloprid	80 mg
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Excipients:

Butylhydroxytoluene (E 321)	0.8 mg
Benzyl alcohol (E 1519)	665.6 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Spot-on solution

Clear yellow to slightly brownish solution

4. CLINICAL PARTICULARS

4.1 Target species

Cats and pet rabbits

4.2 Indications for use, specifying the target species

For cats of 4 kg and greater:

Prevention and treatment of flea (*Ctenocephalides felis*) infestations.

For pet rabbits of 4 kg and greater:

Treatment of flea infestations.

Fleas are killed within one day following treatment. One treatment prevents further flea infestation for three to four weeks on cats and up to one week on pet rabbits. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) in cats, where this has been previously diagnosed by a veterinary surgeon.

4.3 Contraindications

Do not treat unweaned kittens of less than 8 weeks of age.

Do not use on pet rabbits of less than 10 weeks of age.

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

Re-infestation from emergence of new fleas in the environment may continue to occur for six weeks or longer after treatment is initiated. More than one treatment may therefore be required, depending on the level of fleas in the environment. To aid reduction in environmental challenge, the additional use of a suitable environmental treatment against adult fleas and their developing stages is recommended. In order to reduce further the environmental challenge, it is recommended that all cats and rabbits in

the household are treated. Treatment of nursing queens and does controls flea infestations on both dam and offspring.

The product remains effective if the animal becomes wet, for example after exposure to heavy rain. However, re-treatment may become necessary, depending on the presence of fleas in the environment. In these cases do not treat more frequently than once weekly.

4.5 Special precautions for use

Special precautions for use in animals

This product is for topical use and should not be administered orally.

Apply only to undamaged skin.

Care should be taken to avoid the contents of the pipette coming into contact with the eyes or mouth of the recipient animal.

Do not allow recently treated animals to groom each other.

Any collar should be removed prior to application of the product. Prior to re-fitting the collar, the treated area should be visually assessed to ensure it is dry.

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

People with known hypersensitivity to imidacloprid should avoid contact with the product.

This product contains benzyl alcohol and may cause skin sensitisation or transient skin reactions in rare cases (for example, irritation, tingling).

Avoid contact between the product and skin, eyes, or mouth. Do not massage the application site.

Do not eat, drink, or smoke during application.

Wash off any skin contamination with soap and water.

If the product gets into eyes, the eyes should be thoroughly flushed with water.

If skin or eye irritation persists, obtain medical attention.

If the product is accidentally swallowed, obtain medical attention immediately.

After application, do not stroke or groom animals until application site is dry.

Wash hands thoroughly after use.

Other precautions

The solvent in this product may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry before permitting contact with such materials.

4.6 Adverse reactions (frequency and seriousness)

The product is bitter tasting and salivation may occasionally occur if the animal licks the application site immediately after treatment. This is not a sign of intoxication and disappears within some minutes without treatment.

In very rare occasions (less than 1 animal in 10,000 animals, including isolated reports) skin reactions such as hair loss, redness, itching and skin lesions may occur in cats and rabbits. Agitation, excessive salivation and nervous signs such as incoordination, tremors and depression have also been reported but exceptionally in cats.

Oral ingestion may result in other gastro-intestinal signs (vomiting and diarrhoea) which have been observed very rarely based on post marketing data.

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

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- 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

No reproductive toxic effects have been observed in rats and no primary embryotoxic or teratogenic toxic effects have been observed during the studies on rats and rabbits. Studies on pregnant and lactating queens together with their offspring are limited. Evidence so far suggests that no adverse effects are to be expected in these animals.

4.8 Interaction with other medicinal products and other forms of interaction

No incompatibility has been observed between this product at twice the recommended dose and the following commonly used veterinary products: lufenuron, pyrantel and praziquantel (cats). The compatibility of the product was also demonstrated with a wide range of routine treatments under field conditions including vaccination.

4.9 Amounts to be administered and administration route

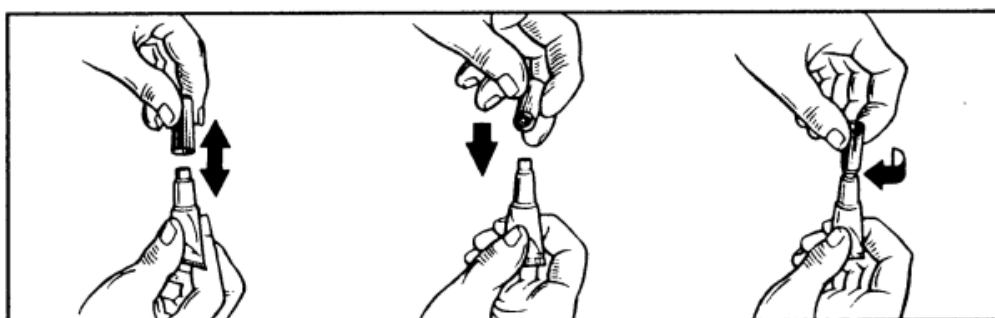
This product is for topical use and should not be administered orally. Animals should be weighed accurately prior to treatment.

Dosage and Treatment Schedule

Cat/Rabbit (kg bw)	Product	Number of Pipettes	Imidacloprid (mg/kg bw)
≥ 4 kg	Advantage 80 for Large Cats and Large Pet Rabbits	1 x 0.8 ml	minimum of 10

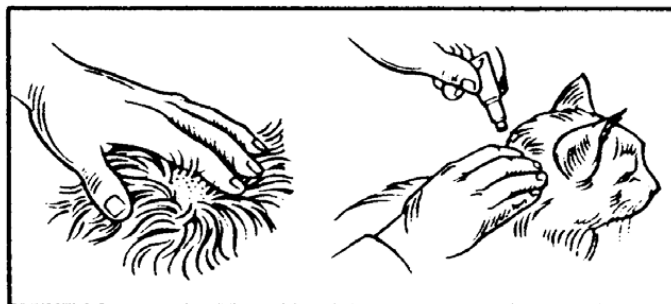
Method of Administration

Remove one pipette from the package. Hold pipette in an upright position, twist and pull off cap. Use reversed cap to twist and remove seal from pipette.



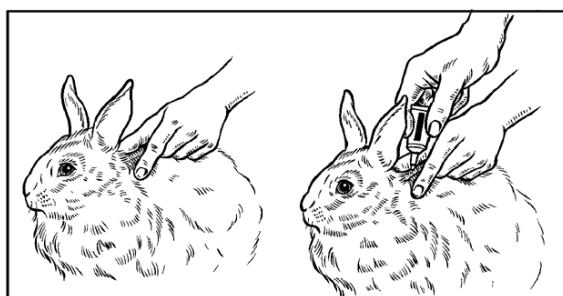
Administration to the Cat

Part the hair on the cat's neck at the base of the skull until the skin is visible. Place the tip of the pipette on the skin and squeeze firmly several times to empty the contents directly onto the skin.



Administration to the Rabbit

Part the hair on the rabbit's neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze firmly several times to empty the contents directly onto the skin.



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

In cats, no adverse clinical signs were produced using doses of five times the therapeutic level weekly for eight consecutive weeks.

In rabbits, no adverse clinical signs were seen using doses of up to 45 mg/kg body weight (4 times the therapeutic level) weekly for 4 consecutive weeks.

In rare cases of overdose or licking of treated fur, nervous system disorders (such as twitching, tremors, ataxia, mydriasis, miosis, lethargy) can occur in cats.

Poisoning following inadvertent oral uptake in animals is unlikely. In this event, treatment should be symptomatic under veterinary medical attention. There is no known specific antidote but administration of activated charcoal may be beneficial.

4.11 Withdrawal period(s)

Do not use on rabbits intended for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Ectoparasiticides for topical use; Imidacloprid
ATCvet code: QP53AX17

5.1 Pharmacodynamic properties

Imidacloprid, 1-(6-Chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine is an ectoparasiticide belonging to a group of chloronicotinyl compounds. Chemically, it is more accurately described as a chloronicotinyl nitroguanidine.

The substance has a high affinity for the nicotinic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS). The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinic receptor sites and the postulated poor penetration through the blood/brain barrier in mammals, it has virtually no effect on the mammalian CNS. The minimal pharmacological activity in mammals is supported by safety studies involving systemic administration of sub-lethal doses to rabbits, mice and rats.

In further studies, in addition to the adulticide flea efficacy of imidacloprid, a larvicidal flea efficacy in the surroundings of the treated pet has been demonstrated. Larval stages in the pet's surroundings are killed following contact with a treated animal.

5.2 Pharmacokinetic particulars

The product is indicated for cutaneous administration. Following topical application in cats, the solution is quickly distributed over the animal. Acute dermal studies in the rat and target animal overdose and serum kinetic studies have established that systemic absorption is very low, transient and not relevant for the clinical efficacy. This has been further demonstrated by a study in which fleas were not killed after having fed on previously treated animals once the animal's skin and fur had been cleaned of all active material.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E 321)
Benzyl alcohol (E 1519)
Propylene carbonate

6.2 Major incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 5 years

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Keep the blister in the outer carton.

6.5 Nature and composition of immediate packaging

Pack sizes 0.8 ml solution per pipette
 Blister pack containing 2, 3, 4, or 6 unit dose pipettes

Container White polypropylene pipettes with caps

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 products should be disposed of in accordance with local requirements. The product should not enter

water courses as this may be dangerous for fish and other aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed in accordance with national requirements after conclusion of the MR phase]
{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

[to be completed in accordance with national requirements after conclusion of the MR phase]
{MM/YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton, pack size of 2, 3, 4 and 6 pipettes.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 80 mg feline and bunny Spot-on solution [UK]

Advantage 80 mg Spot-on solution for Large Cats and Large Pet Rabbits [AT, DE, FR, IE, IT]

Imidacloprid

2. STATEMENT OF ACTIVE SUBSTANCES

Each 0.8 ml pipette contains:

Active substance: 80 mg imidacloprid;

0.8 mg butylhydroxytoluene (E 321)

665.6 mg benzyl alcohol (E 1519)

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

2 pipettes (2x 0.8 ml)

3 pipettes (3x 0.8 ml)

4 pipettes (4x 0.8 ml)

6 pipettes (6x 0.8 ml)

5. TARGET SPECIES

Cats and pet rabbits

6. INDICATION(S)

Flea (*Ctenocephalides felis*) prevention and treatment for cats of 4 kg and greater.

Flea treatment for pet rabbits of 4 kg and greater.

One treatment prevents further flea infestation for three to four weeks on cats and up to one week on pet rabbits. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) in cats, where this has been previously diagnosed by a veterinary surgeon.



[Pictogram – flea]

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For external use only.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Do not use on rabbits intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

Do not treat unweaned kittens of less than 8 weeks of age.

Do not use on pet rabbits of less than 10 weeks of age.

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

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. The product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.

[Prescription status to be completed nationally; Blue Box]

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

[MAH to be completed nationally]

Manufactured by
KVP Pharma + Veterinär Produkte GmbH
Projensdorfer Str. 324, 24106 Kiel
Germany

16. MARKETING AUTHORISATION NUMBER(S)
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[to be completed nationally]

17. MANUFACTURER'S BATCH NUMBER
--

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**Pipette label****1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Advantage

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Imidacloprid(e) 80 mg

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

0.8 ml

4. ROUTE(S) OF ADMINISTRATION**5. WITHDRAWAL PERIOD(S)****6. BATCH NUMBER**

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

[Cat-Pictogram]



≥ 4kg

[Rabbit-Pictogram]



≥ 4kg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 80mg feline and bunny Spot-on solution [UK]

Advantage 80 mg Spot-on solution for Large Cats and Large Pet Rabbits [AT, DE, FR, IE, IT]

Imidacloprid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Lot {number}

5. THE WORDS “FOR ANIMAL TREATMENT ONLY”

[Cat-Pictogram]



≥ 4kg

[Rabbit-Pictogram]



≥ 4kg
0.8 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Advantage Spot-on solution for Cats and Pet Rabbits

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

Marketing authorisation holder:
[to be completed nationally]

Manufacturer responsible for batch release:
KVP Pharma + Veterinär Produkte GmbH
Projensdorfer Str. 324, 24106 Kiel
Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 40 mg feline and bunny Spot-on solution [UK]
Advantage 80 mg feline and bunny Spot-on solution [UK]
Advantage 40 mg Spot-on solution for Small Cats and Small Pet Rabbits [AT, DE, FR, IE, IT]
Advantage 80 mg Spot-on solution for Large Cats and Large Pet Rabbits [AT, DE, FR, IE, IT]

Imidacloprid

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

Each pipette of clear yellow to slightly brownish solution contains:

	0.4 ml	0.8 ml
Active substance		
Imidacloprid	40 mg	80 mg
Excipients:		
Butylhydroxytoluene (E321)	0.4 mg	0.8 mg
Benzyl alcohol (E1519)	332.8 mg	665.6 mg

4. INDICATION(S)

For the prevention and treatment of flea (*Ctenocephalides felis*) infestations on cats and for the treatment of flea infestations on pet rabbits.

Fleas are killed within one day following treatment. One treatment prevents further flea infestation for three to four weeks on cats and up to one week on pet rabbits. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) in cats, where this has been previously diagnosed by a veterinary surgeon.

5. CONTRAINDICATIONS

Do not treat unweaned kittens of less than 8 weeks of age.

Do not use on pet rabbits of less than 10 weeks of age.

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

6. ADVERSE REACTIONS

The product is bitter tasting and salivation may occasionally occur if the animal licks the application site immediately after treatment. This is not a sign of intoxication and disappears within some minutes without treatment.

In very rare occasions (less than 1 animal in 10,000 animals, including isolated reports) skin reactions such as hair loss, redness, itching and skin lesions may occur in cats and rabbits. Agitation, excessive salivation and nervous signs such as incoordination, tremors and depression have also been reported but exceptionally in cats.

Oral ingestion may result in other gastro-intestinal signs (vomiting and diarrhoea) which have been observed very rarely based on post marketing data.

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

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- 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 pet rabbits

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

This product is for topical use and should not be administered orally. Animals should be weighed accurately prior to treatment.

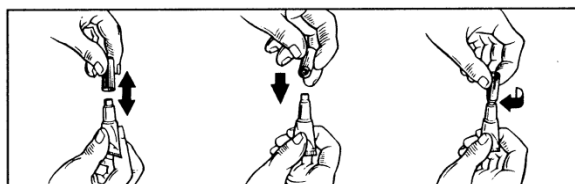
Any instructions given by a veterinary surgeon for the use of this product should be followed.

Dosage and Treatment Schedule

Cat/Rabbit (kg bw)	Product	Number of Pipettes	Imidacloprid (mg/kg bw)
< 4 kg	Advantage 40 for Small Cats and Small Pet Rabbits	1 x 0.4 ml	minimum of 10
≥ 4 kg	Advantage 80 for Large Cats and Large Pet Rabbits	1 x 0.8 ml	minimum of 10

Method of Administration

Remove one pipette from the package. Hold pipette in an upright position, twist and pull off cap. Use reversed cap to twist and remove seal from pipette.



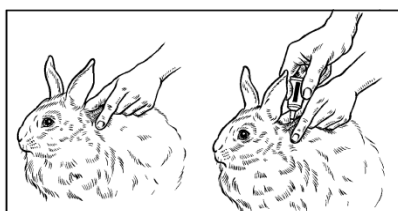
Administration to the Cat

Part the hair on the cat's neck at the base of the skull until the skin is visible. Place the tip of the pipette on the skin and squeeze firmly several times to empty the contents directly onto the skin.



Administration to the Rabbit

Part the hair on the rabbit's neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze firmly several times to empty the contents directly onto the skin.



9. ADVICE ON CORRECT ADMINISTRATION

For external use only.

Application at the base of the skull will minimize the opportunity for the cat to lick the product, please also refer to section *Adverse Reactions*.

Apply only to undamaged skin. Do not allow recently treated animals to groom each other.

10. WITHDRAWAL PERIOD(S)

Do not use on rabbits intended for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Keep the blister in the outer carton.

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

12. SPECIAL WARNING(S)

Special warnings for each target species:

Re-infestation from emergence of new fleas in the environment may continue to occur for six weeks or longer after treatment is initiated. More than one treatment may therefore be required, depending on the level of fleas in the environment. To aid in environmental challenge, the additional use of a suitable environmental treatment against adult fleas and their developing stages is recommended. In order to reduce further the environmental challenge, it is recommended that all cats and rabbits in the household are treated. Treatment of nursing queens and does controls flea infestations on both dam and offspring.

The product remains effective if the animal becomes wet, for example after exposure to heavy rain. However, re-treatment may become necessary, depending on the presence of fleas in the environment. In these cases do not re-treat more frequently than once weekly.

Special precautions for use in animals:

This product is for topical use and should not be administered orally.

Apply only to undamaged skin

Care should be taken to avoid the contents of the pipette coming into contact with the eyes or mouth of the recipient animal.

Do not allow recently treated animals to groom each other.

Any collar should be removed prior to application of the product.

Prior to re-fitting the collar, the treated area should be visually assessed to ensure it is dry.

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

People with known hypersensitivity to imidacloprid should avoid contact with the product.

This product contains benzyl alcohol and may cause skin sensitisation or transient skin reactions in rare cases (for example, irritation, tingling).

Avoid contact between the product and skin, eyes, or mouth. Do not massage the application site.

Do not eat, drink, or smoke during application.

Wash off any skin contamination with soap and water.

If the product gets into eyes, the eyes should be thoroughly flushed with water.

If skin or eye irritation persists, obtain medical attention.

If the product is accidentally swallowed, obtain medical attention immediately.

After application, do not stroke or groom animals until application site is dry.

Wash hands thoroughly after use.

Pregnancy and lactation:

No reproductive toxic effects have been observed in rats and no primary embryotoxic or teratogenic toxic effects have been observed during the studies on rats and rabbits. Studies on pregnant and lactating queens together with their offspring are limited. Evidence so far suggests that no adverse effects are to be expected in these animals.

Interaction with other medicinal products and other forms of interaction:

No incompatibility has been observed between this product at twice the recommended dose and the following commonly used veterinary products: lufenuron, pyrantel and praziquantel (cats). The compatibility of the product was also demonstrated with a wide range of routine treatments under field conditions including vaccination.

Overdose (symptoms, emergency procedures, antidotes):

In cats, no adverse clinical signs were produced using doses of five times the therapeutic level weekly for eight consecutive weeks.

In rabbits, no adverse clinical signs were seen using doses of up to 45 mg/kg body weight (4 times the therapeutic level) weekly for 4 consecutive weeks.

In rare cases of overdose or licking of treated fur, nervous system disorders (such as twitching, tremors, ataxia, mydriasis, miosis, lethargy) can occur in cats.

Poisoning following inadvertent oral uptake in animals is unlikely. In this event, treatment should be symptomatic under veterinary medical attention. There is no known specific antidote but administration of activated charcoal may be beneficial.

Incompatibilities:

None known.

Other precautions:

The solvent in this product may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry before permitting contact with such materials.

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

[to be adapted nationally, if required]

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. The product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

In further studies, in addition to the adulticide flea efficacy of imidacloprid, a larvicidal flea efficacy in the surroundings of the treated pet has been demonstrated. Larval stages in the pet's surroundings are killed following contact with a treated animal.

Pack sizes	0.4 ml / 0.8 ml solution per pipette; blister pack containing 2, 3, 4, or 6 unit dose pipettes
Container	White polypropylene pipettes with caps

Not all pack sizes may be marketed.

[Further information like prescription status or marketing authorisation numbers to be completed nationally, if required]