SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 400 Spot-on solution for Dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Imidacloprid 400 mg/pipette (4.0 ml of a 10 % solution)

Excipient(s):
Butylhydroxytoluene (E 321) 4.0 mg/pipette

For a 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

Dogs

4.2 Indications for use, specifying the target species

For the prevention and treatment of flea infestations and for the treatment of biting lice *(Trichodectes canis)* on dogs of 25 kg body weight and greater.
For dogs less than 25 kg body weight, use the appropriate Advantage for Dogs product (see section 4.9).
Fleas on dogs are killed within one day following treatment. One treatment prevents further flea infestation for four weeks. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon.

4.3 Contraindications

Do not treat unweaned puppies of less than 8 weeks of age.
Do not use in animals that are known to be hypersensitive to the active substance or any of the excipients

4.4 Special warnings

None.

4.5 Special precautions for use

Special precautions for use in animals

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

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

Wash hands thoroughly after use.
Wash off any skin contamination with soap and water.
People with known skin sensitivity may be particularly sensitive to this product.
Avoid contact of the product with the eyes or mouth.
If the product gets into eyes accidentally, the eyes should be thoroughly flushed with water. If skin or eye irritation persists, or the product is accidentally swallowed, obtain medical attention.
Do not eat, drink or smoke during application.

Other precautions

Imidacloprid is toxic to aquatic organisms. To avoid adverse effects on aquatic organisms, treated dogs should not be allowed to enter surface water for 48 hours after treatment.

4.6 Adverse reactions (frequency and seriousness)

The product is bitter tasting and salivation may occasionally occur if the dog licks the application site immediately after treatment. This is not a sign of intoxication and disappears within some minutes without treatment (see also section 4.9 *Amounts to be administered and administration route*).
In very rare occasions skin reactions such as hair loss, redness, itching and skin lesions may occur. Agitation and disorientation has also been reported. Excessive salivation and nervous signs such as incoordination, tremors and depression have been reported exceptionally in dogs.

4.7 Use during pregnancy, lactation or lay

No primary embryotoxic, teratogenic or reproductive toxic effects have been observed during the studies with imidacloprid on rats and rabbits. Studies on pregnant and lactating bitches 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: fenthion, lufenuron, milbemycin, febantel, pyrantel and praziquantel. 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

Dosage and Treatment Schedule

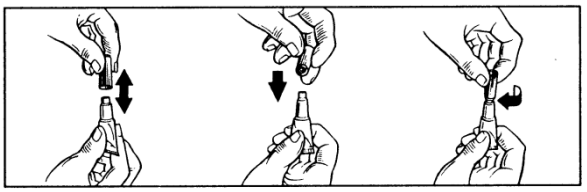
Dog (kg bw)	Product	Number of Pipettes	Imidacloprid (mg/kg bw)
< 4 kg	Advantage 40 for Dogs	1 x 0.4 ml	minimum of 10
≥ 4 < 10 kg	Advantage 100 for Dogs	1 x 1.0 ml	minimum of 10
≥ 10 < 25 kg	Advantage 250 for Dogs	1 x 2.5 ml	minimum of 10
≥ 25 < 40 kg	Advantage 400 for Dogs	1 x 4.0 ml	minimum of 10
≥ 40 kg	Advantage 400 for Dogs	2 x 4.0 ml	minimum of 10

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.

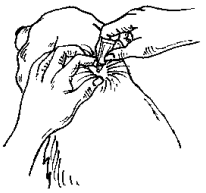
The product remains effective if the animal becomes wet, for example after swimming or exposure to heavy rain. However, in cases of frequent swimming or bathing re-treatment may become necessary, depending on the presence of fleas in the environment. In these cases do not re-treat more frequently than once weekly.
In case of biting louse infestation, a further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment.

Method of Administration

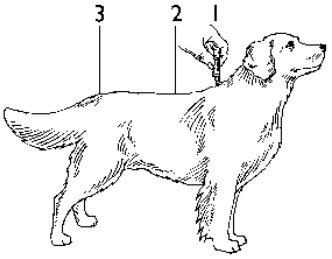
Remove one pipette from the package. For dogs of 40 kg body weight and greater use two pipettes. Hold pipette in an upright position, twist and pull off cap. Use reversed cap to twist and remove seal from pipette.



For dogs less than 25 kg body weight:
With the dog in the standing position, part the coat between the shoulder blades 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.



For dogs of 25 kg body weight and greater:
The dog should be standing for easy application. The entire contents of the pipette(s) should be applied evenly to three or four spots all located at different application sites along the dog's backline from the shoulder to the base of the tail. At each spot part the coat until the skin is visible.



Place the tip of the pipette on the skin and gently squeeze to expel a portion of the contents directly onto the skin.

For all dogs:
Do not apply an excessive amount of solution at any one spot that could cause some of the solution to run off the side of the dog.

The product is bitter tasting and salivation may occasionally occur if the dog licks the application site immediately after treatment. This is not a sign of intoxication and disappears within some minutes without treatment. Correct application will minimize the opportunity for the dog to lick the product.

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

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

No adverse clinical signs were produced by either individual doses of up to 200 mg/kg body weight (five to eight times the therapeutic dose), daily treatments at 100 mg/kg body weight for five consecutive days or weekly treatments at five times the maximum dose rate for eight 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.

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)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiparasitic products, insecticides and repellents
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

The substance has a high affinity for the nicotinergic 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 nicotinergic 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 dogs, 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

* CAS-No. 138261-41-3

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 E321
Benzyl alcohol
Propylene carbonate

6.2 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

No special precautions required.
Store away from food, drink and animal feeding stuffs.

6.5 Nature and composition of immediate packaging

Pack sizes	4.0 ml solution per pipette Pack containing 1, 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 product or waste materials should be disposed of in accordance with national requirements.

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]

10. DATE OF REVISION OF THE TEXT

[to be completed in accordance with national requirements after conclusion of the MR phase]

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton, pack size of 1, 2, 3, 4 and 6 pipettes

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 400 for Dogs

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Each 4.0 ml pipette contains:
Active substance: 400 mg imidacloprid;
4.0 mg butylhydroxytoluene.

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette	(1x 4.0 ml)
2 pipettes	(2x 4.0 ml)
3 pipettes	(3x 4.0 ml)
4 pipettes	(4x 4.0 ml)
6 pipettes	(6x 4.0 ml)

5. TARGET SPECIES

Dogs

6. INDICATION(S)

Flea prevention and flea and biting louse (*Trichodectes canis)* treatment for dogs of 25 kg and greater. Fleas on dogs are killed within one day following treatment. One treatment prevents further flea infestation for four weeks. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For external use only.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.
Do not treat unweaned puppies of less than 8 weeks of age.
Keep the blister in the outer carton.

10. EXPIRY DATE

Expiry/EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

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

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 REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight 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)

[MAH to be completed nationally]

17. MANUFACTURER'S BATCH NUMBER

Batch/Lot {number}

[Pictograms]

Flea

Louse

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)

10% imidacloprid(e)

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

4.0 ml

4. ROUTE(S) OF ADMINISTRATION

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

[Dog-Pictogram]

≥ 25 kg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{Blister}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

[Dog-Pictogram]

≥ 25 kg

4.0 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET
Advantage Spot-on solution 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
[to be completed nationally]

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

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advantage 40 Spot-on solution for Dogs
Advantage 100 Spot-on solution for Dogs
Advantage 250 Spot-on solution for Dogs
Advantage 400 Spot-on solution for Dogs
Imidacloprid

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

Active substance:
10 % (100 mg/ml) Imidacloprid

Excipient(s):
0.1 % (1 mg/ml) Butylhydroxytoluene (E 321)
Benzyl alcohol

Each pipette contains:

	Pipette	**Imidacloprid**	**E321**
Advantage 40 for Dogs (< 4 kg)	0.4 ml	40 mg	0.4 mg
Advantage 100 for Dogs (≥ 4 < 10 kg)	1.0 ml	100 mg	1.0 mg
Advantage 250 for Dogs (≥ 10 < 25 kg)	2.5 ml	250 mg	2.5 mg
Advantage 400 for Dogs (≥ 25 kg)	4.0 ml	400 mg	4.0 mg

4. INDICATION(S)

For the prevention and treatment of flea infestations and for the treatment of biting lice (*Trichodectes canis)* on dogs.
Fleas on dogs are killed within one day following treatment. One treatment prevents further flea infestation for four weeks. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon.

5. CONTRAINDICATIONS

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

Do not use in animals that are known to be hypersensitive to the active substance or any of the excipients

6. ADVERSE REACTIONS

The product is bitter tasting and salivation may occasionally occur if the dog 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 skin reactions such as hair loss, redness, itching and skin lesions may occur. Agitation and disorientation has also been reported. Excessive salivation and nervous signs such as incoordination, tremors and depression have been reported exceptionally in dogs.

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

7. TARGET SPECIES

Dogs

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

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

Dosage and Treatment Schedule

Dog (kg bw)	Product	Number of Pipettes	Imidacloprid (mg/kg bw)
Less than 4 kg	Advantage 40 for Dogs	1 x 0.4 ml	minimum of 10
4 to less than 10 kg	Advantage 100 for Dogs	1 x 1.0 ml	minimum of 10
10 to less than 25 kg	Advantage 250 for Dogs	1 x 2.5 ml	minimum of 10
25 to less than 40 kg	Advantage 400 for Dogs	1 x 4.0 ml	minimum of 10
40 kg and greater	Advantage 400 for Dogs	2 x 4.0 ml	minimum of 10

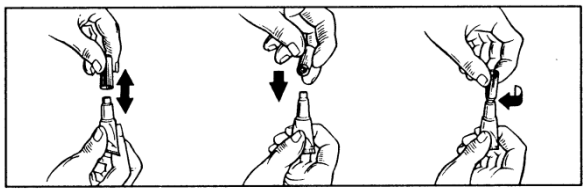
Re-infestation from emergence of new fleas in the environment may continue to occur for six weeks or longer after treatment is initiated. More than one treatment may therefore be required, depending on the level of fleas in the environment. To aid in environmental challenge, the additional use of a suitable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

The product remains effective if the animal becomes wet, for example after swimming or exposure to heavy rain. However, in cases of frequent swimming or bathing 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.

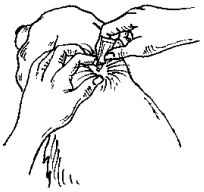
In case of biting louse infestation, a further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment.

Method of Administration

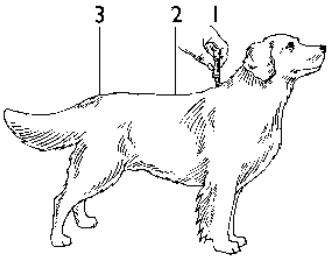
Remove one pipette from the package. For dogs of 40 kg body weight and greater use two pipettes (Advantage 400 for Dogs). Hold pipette in an upright position, twist and pull off cap. Use reversed cap to twist and remove seal from pipette.



For dogs less than 25 kg body weight:
With the dog in the standing position, part the coat between the shoulder blades 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.



For dogs of 25 kg body weight and greater:
The dog should be standing for easy application. The entire contents of the pipette(s) should be applied evenly to three or four spots all located at different application sites along the dog´s backline from the shoulder to the base of the tail. At each spot part the coat until the skin is visible.



Place the tip of the pipette on the skin and gently squeeze to expel a portion of the contents directly onto the skin.

9. ADVICE ON CORRECT ADMINISTRATION

For external use only.
Do not apply an excessive amount of solution at any one spot that could cause some of the solution to run off the side of the dog.
Correct application will minimize the opportunity for the dog 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

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.

Store away from food, drink and animal feeding stuffs.
Keep the blister in the outer carton.

12. SPECIAL WARNING(S)

Special precautions for use in animals

This product is for topical use and should not be administered orally.
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.
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.
Imidacloprid is toxic to aquatic organisms. To avoid adverse effects on aquatic organisms, treated dogs should not be allowed to enter surface water for 48 hours after treatment.

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

Wash hands thoroughly after use.
Wash off any skin contamination with soap and water.
People with known skin sensitivity may be particularly sensitive to this product.
Avoid contact of the product with the eyes or mouth.
If the product gets into eyes accidentally, the eyes should be thoroughly flushed with water. If skin or eye irritation persists, or the product is accidentally swallowed, obtain medical attention.
Do not eat, drink or smoke during application.

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

[to be adapted nationally, if required]
Any unused product or waste materials should be disposed of in accordance with national requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Pack sizes 0.4 / 1.0 / 2.5 / 4.0 ml solution per pipette
Pack containing 1, 2, 3, 4, or 6 unit dose pipettes

Not all pack sizes may be marketed.

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.

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.

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

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

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