ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 40 mg + 4 mg spot-on solution for small cats and ferrets
Advocate 80 mg + 8 mg spot-on solution for large cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Advocate for cats contains 100 mg/ml imidacloprid and 10 mg/ml moxidectin.

Each unit dose (pipette) contains:

	Unit dose	Imidacloprid	Moxidectin
Advocate for small cats (≤ 4 kg) and ferrets	0.4 ml	40 mg	4 mg
Advocate for large cats (> 4–8 kg)	0.8 ml	80 mg	8 mg

Excipients:

Benzyl alcohol
Butylhydroxytoluene 1 mg/ml (E 321; as antioxidant).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Spot-on solution.
Clear yellow to brownish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cats, ferrets

4.2 Indications for use, specifying the target species

For cats suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of ear mite infestation (*Otodectes cynotis*),
- the treatment of notoedric mange (*Notoedres cati*),
- the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) (adults),
- the prevention of lungworm disease (L3/L4 larvae of *Aelurostrongylus abstrusus*),
- the treatment of the lungworm *Aelurostrongylus abstrusus* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* and *Ancylostoma tubaeforme*).
  The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

For ferrets suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),

- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*).

4.3 Contraindications

Do not use in kittens under 9 weeks of age.

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

For ferrets: Do not use Advocate for large cats (0.8 ml) or Advocate for dogs (any size).

For dogs, the corresponding "Advocate for dog" product, which contains 100 mg/ml imidacloprid and 25 mg/ml moxidectin, must be used.

Do not use on canaries.

4.4 Special warnings for each target species

Please refer to section 4.5.

The product's efficacy has not been tested in ferrets weighing over 2 kg and therefore the duration of effect might be shorter in these animals.

Brief contact of the animal with water on one or two occasions between monthly treatments is unlikely to significantly reduce the efficacy of the product. However, frequent shampooing or immersion of the animal in water after treatment may reduce the efficacy of the product.

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see also sections 4.2 and 4.9).

4.5 Special precautions for use

Special precautions for use in animals

The treatment of cats weighing less than 1 kg and ferrets weighing less than 0.8 kg should be based on a benefit-risk assessment.

There is limited experience on the use of the product in sick and debilitated animals, thus the product should only be used based on a benefit-risk assessment for these animals.

Do not apply in the mouth, in the eyes or the ears of the animal.

Care should be taken that the product is not ingested by animals and does not come into contact with the eyes or mouth of the recipient and/or other animals.

Consider carefully the correct application method described in section 4.9, especially that the product should be applied to the site specified in order to minimise the risk for the animal to lick the product.

Do not allow recently treated animals to groom each other. Do not allow treated animals to come into contact with untreated animals until the application site is dry.

It is recommended that cats and ferrets living in, or travelling to areas endemic for heartworm are treated monthly with the product to protect them from heartworm disease.

Whilst the accuracy of diagnosis of heartworm infection is limited, it is recommended that attempts be made to check the heartworm status of any cat and ferret aged over 6 months, before beginning prophylactic treatment, as use of the product on cats or ferrets which have adult heartworms may cause serious adverse effects, including death. If adult heartworm infection is diagnosed, the infection should be treated in accordance with current scientific knowledge.

In certain individual cats *Notoedres cati* infestation may be severe. In these severe cases concomitant supportive treatment is necessary as treatment with the product alone may not be sufficient to prevent death of the animal.

Imidacloprid is toxic for birds, especially canaries.

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

Avoid contact with skin, eyes or mouth.
Do not eat, drink or smoke during application.
Wash hands thoroughly after use.
After application do not stroke or groom animals until the application site is dry.
In case of accidental spillage onto skin, wash off immediately with soap and water.
People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In very rare cases the product may cause skin sensitisation or transient skin reactions (for example numbness, irritation or burning/tingling sensation).
In very rare cases the product may cause respiratory irritation in sensitive individuals.
If the product accidentally gets into eyes, they should be thoroughly flushed with water.
If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical advice immediately and show the package leaflet or the label to the physician.

The solvent in Advocate may stain or damage 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)

Use of the product may result in transient pruritus in cats. On rare occasions greasy fur, erythema and vomiting can occur. These signs disappear without further treatment. The product may, in rare cases, cause local hypersensitivity reactions. If the animal licks the application site after treatment, neurological signs (most of which are transient) may be observed in very rare cases (see section 4.10).

The product tastes bitter. 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. Correct application will minimise licking of the application site.

The product may in very rare cases cause at the application site a sensation resulting in transient behavioural changes such as lethargy, agitation, and inappetence.

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

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in the target species. Therefore, the use of the product is not recommended in animals intended for breeding or during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

During treatment with Advocate no other antiparasitic macrocyclic lactone should be administered.

No interactions between Advocate and routinely used veterinary medicinal products or medical or surgical procedures have been observed.

4.9 Amounts to be administered and administration route

Dosage schedule for cats:

The recommended minimum doses are 10 mg/kg bodyweight imidacloprid and 1.0 mg/kg bodyweight moxidectin, equivalent to 0.1 ml/kg bodyweight Advocate for cats.

The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation.

Weight of cat [kg]	Pipette size to be used	Volume [ml]	Imidacloprid [mg/kg bw]	Moxidectin [mg/kg bw]
≤ 4 kg	Advocate for small cats	0.4	minimum of 10	minimum of 1
> 4–8 kg	Advocate for large cats	0.8	10–20	1–2
> 8 kg	the appropriate combination of pipettes			

Flea treatment and prevention (*Ctenocephalides felis*)

One treatment prevents future flea infestation for 4 weeks. Existing pupae in the environment may emerge for 6 weeks or longer after treatment is initiated, depending upon climatic conditions. Therefore, it may be necessary to combine Advocate treatment with environmental treatments aimed at breaking the flea life cycle in the surroundings. This can result in a more rapid reduction in the household flea population. The product should be administered at monthly intervals when used as part of a treatment strategy for flea allergy dermatitis.

Treatment of ear mite infestation (Otodectes cynotis)

A single dose of the product should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment. Do not apply directly to the ear canal.

Treatment of notoedric mange (Notoedres cati)

A single dose of the product should be administered.

Treatment of the lungworm Eucoleus aerophilus (syn. Capillaria aerophila) (adults)

A single dose of the product should be administered.

Prevention of Aelurostrongylus abstrusus

The product should be administered monthly.

Treatment of Aelurostrongylus abstrusus

Advocate should be administered monthly for three consecutive months.

Treatment of the eye worm Thelazia callipaeda (adults)

A single dose of the product should be administered.

Heartworm prevention (Dirofilaria immitis)

Cats in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in section 4.5 should be considered.

For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit heartworm larvae) are present. The product may be administered throughout the year. The first dose may be given after first possible exposure to mosquitoes, but not more than one month after this exposure. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with Advocate must be given within 1 month of the last dose of the former medication.

In non-endemic areas there should be no risk of cats having heartworm. Therefore, they can be treated without special precautions.

Roundworm and hookworm treatment (Toxocara cati and Ancylostoma tubaeforme)

In areas endemic for heartworm, monthly treatment may significantly reduce the risk of re-infection caused by the respective roundworms and hookworms. In areas non-endemic for heartworm, the product can be used as part of a seasonal prevention programme against fleas and gastrointestinal nematodes.

Dosage schedule for ferrets:

One pipette of Advocate spot-on solution for Small Cats (0.4 ml) should be administered per animal. Do not exceed the recommended dose.
The treatment schedule should be based on the local epidemiological situation.

Flea treatment and prevention (Ctenocephalides felis)

One treatment prevents future flea infestation for 3 weeks. Under heavy flea pressure it may be necessary to repeat administration after 2 weeks.

Heartworm prevention (Dirofilaria immitis)

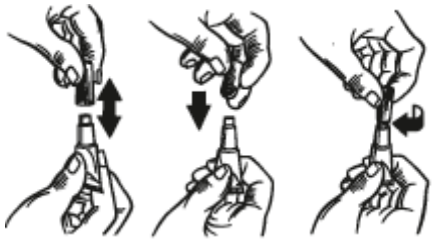
Ferrets in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in section 4.5 should be considered.

For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit heartworm larvae) are present. The product may be administered throughout the year. The first dose may be given after first possible exposure to mosquitoes, but not more than one month after this exposure. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes.
In non-endemic areas there should be no risk of ferrets having heartworm. Therefore, they can be treated without special precautions.

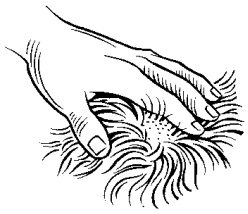
Method of administration

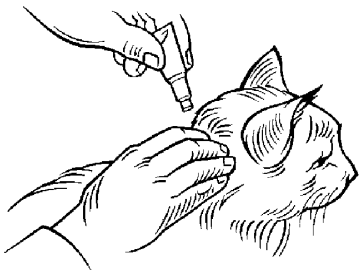
For external use only.

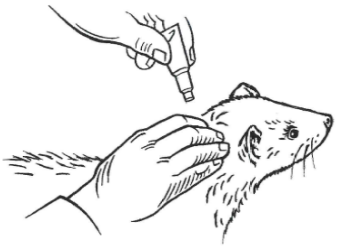
Remove one pipette from the package. Then hold the pipette in an upright position, and twist and pull off the cap. Reverse the cap and use it to twist and remove the seal from the pipette, as shown.



Part the fur on the animal's neck at the base of the skull until the skin is visible. Place the tip of the pipette on the skin and squeeze the pipette firmly several times to empty its contents directly onto the skin. Application at the base of the skull will minimise the opportunity for the animal to lick the product. Apply only to undamaged skin.







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

Up to 10 times the recommended dose was tolerated in cats with no evidence of adverse effects or undesirable clinical signs.
The product was administered to kittens at up to 5 times the recommended dose, every 2 weeks for 6 treatments, and there were no serious safety concerns. Transient mydriasis, salivation, vomiting and transient rapid respiration were observed.
After accidental oral ingestion or overdose, neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur in very rare cases.

The product was administered to ferrets at 5 times the recommended dose, every 2 weeks for 4 treatments, and there was no evidence of adverse effects or undesirable clinical signs.

In case of accidental oral uptake, symptomatic treatment should be administered. There is no known specific antidote. The use of activated charcoal may be beneficial.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiparasitic products, insecticides and repellents, macrocyclic lactones, milbemycins.
ATCvet code: QP54AB52.

5.1 Pharmacodynamic properties

Imidacloprid, 1-(6-Chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Chemically, it is more accurately described as a chloronicotinyl nitroguanidine. Imidacloprid is effective against larval flea stages and adult fleas. Flea larvae in the pet's surroundings are killed after contact with a pet treated with the product. Imidacloprid has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) of the flea. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinergic receptors and the postulated poor penetration through the blood-brain barrier in mammals, it has virtually no effect on the mammalian CNS. Imidacloprid has minimal pharmacological activity in mammals.

Moxidectin, 23-(O-methyloxime)-F28249 alpha is a second-generation macrocyclic lactone of the milbemycin family. It is a parasiticide which is active against many internal and external parasites. Moxidectin is active against larval stages (L3, L4) of *Dirofilaria immitis.* It is also active against gastrointestinal nematodes. Moxidectin interacts with GABA and glutamate-gated chloride channels. This leads to opening of the chloride channels on the postsynaptic junction, the inflow of chloride ions and induction of an irreversible resting state. The result is flaccid paralysis of affected parasites, followed by their death and/or expulsion. The product has a persistent action and protects cats for 4 weeks after a single application against reinfection with *Dirofilaria immitis*.

5.2 Pharmacokinetic particulars

After topical administration of the product, imidacloprid is rapidly distributed over the animal's skin within one day of application. It can be found on the body surface throughout the treatment interval. Moxidectin is absorbed through the skin, reaching maximum plasma concentrations approximately 1 to 2 days after treatment in cats. Following absorption from the skin, moxidectin is distributed systemically throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. It is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month.

The mean T ½ in cats ranges between 18.7 and 25.7 days.
Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in cats.

Environmental properties

See section 6.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Butylhydroxytoluene
Propylene carbonate

6.2 Major incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and composition of immediate packaging

Container material	White polypropylene unit dose pipette with screw cap.
Pack sizes	0.4 ml and 0.8 ml per pipette. Blister pack containing 1, 2, 3, 4, 6, 9, 12, 21 or 42 unit dose pipettes.

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

Advocate should not enter water courses as this may be dangerous for fish and other aquatic organisms.
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH
51368 Leverkusen
GERMANY

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/001-004, EU/2/03/039/013-014, EU/2/03/039/019-022, EU/2/03/039/031-038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02/04/2003.
Date of last renewal: 14/01/2013.

10. DATE OF REVISION OF THE TEXT

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

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 40 mg + 10 mg spot-on solution for small dogs
Advocate 100 mg + 25 mg spot-on solution for medium dogs
Advocate 250 mg + 62.5 mg spot-on solution for large dogs
Advocate 400 mg + 100 mg spot-on solution for extra-large dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Advocate for dogs contains 100 mg/ml imidacloprid and 25 mg/ml moxidectin.

Each unit dose (pipette) contains:

	Unit dose	Imidacloprid	Moxidectin
Advocate for small dogs (≤ 4 kg)	0.4 ml	40 mg	10 mg
Advocate for medium dogs (> 4–10 kg)	1.0 ml	100 mg	25 mg
Advocate for large dogs (> 10–25 kg)	2.5 ml	250 mg	62.5 mg
Advocate for extra-large dogs (> 25–40 kg)	4.0 ml	400 mg	100 mg

Excipients:

Benzyl alcohol
Butylhydroxytoluene 1 mg/ml (E 321; as antioxidant).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Spot-on solution.
Clear yellow to brownish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

For dogs suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of biting lice (*Trichodectes canis*),
- the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of circulating microfilariae (*Dirofilaria immitis*),
- the treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*)
- the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*),
- the reduction of circulating microfilariae (*Dirofilaria repens*),

- the prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*),
- the treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*,
- the prevention of spirocercosis (*Spirocerca lupi*),
- the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara canis, Ancylostoma caninum* and *Uncinaria stenocephala*, adults of *Toxascaris leonina* and *Trichuris vulpis*).
  The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

4.3 Contraindications

Do not use in puppies under 7 weeks of age.

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

Do not use in dogs classified as Class 4 for heartworm disease as the safety of the product has not been evaluated in this animal group.

For cats, the corresponding "Advocate for cats" product (0.4 or 0.8 ml), which contains 100 mg/ml imidacloprid and 10 mg/ml moxidectin, must be used.

For ferrets: Do not use Advocate for dogs. Only "Advocate for small cats and ferrets" (0.4 ml) must be used.

Do not use on canaries.

4.4 Special warnings for each target species

Please refer to section 4.5.

Brief contact of the animal with water on one or two occasions between monthly treatments is unlikely to significantly reduce the efficacy of the product. However, frequent shampooing or immersion of the animal in water after treatment may reduce the efficacy of the product.

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see also sections 4.2 and 4.9).

Efficacy against adult *Dirofilaria repens* has not been tested under field conditions.

4.5 Special precautions for use

Special precautions for use in animals

The treatment of animals weighing less than 1 kg should be based on a benefit-risk assessment.

There is limited experience on the use of the product in sick and debilitated animals, thus the product should only be used based on a benefit-risk assessment for these animals.

Do not apply in the mouth, in the eyes or the ears of the animal.

Care should be taken that the product is not ingested by animals and does not come into contact with the eyes or mouth of the recipient and/or other animals.

Consider carefully the correct application method described in section 4.9, especially that the product should be applied to the site specified in order to minimise the risk for the animal to lick the product.

Do not allow recently treated animals to groom each other. Do not allow treated animals to come into contact with untreated animals until the application site is dry.

When the product is applied in 3 to 4 separate spots (see section 4.9), specific care should be taken to prevent the animal licking the application sites.

This product contains moxidectin (a macrocyclic lactone), therefore special care should be taken with Collie or Old English Sheep dogs and related breeds or crossbreeds, to correctly administer the product as described under section 4.9; in particular, oral uptake by Collie or Old English Sheep dogs and related breeds or crossbreeds should be prevented.

Advocate should not enter water courses as it has harmful effects on aquatic organisms: moxidectin is highly toxic to aquatic organisms. Dogs should not be allowed to swim in surface waters for 4 days after treatment.

The safety of the product has only been evaluated in dogs classified as either Class 1 or 2 for heartworm disease in laboratory studies and in a few Class 3 dogs in a field study. Therefore the use in dogs with obvious or severe symptoms of the disease should be based on a careful benefit-risk assessment by the treating veterinarian.

Although experimental overdosage studies have shown that the product may be safely administered to dogs infected with adult heartworms, it has no therapeutic effect against adult *Dirofilaria immitis*. It is therefore recommended that all dogs 6 months of age or more, living in areas endemic for heartworm, should be tested for existing adult heartworm infection before being treated with the product. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of Advocate has not been evaluated when administered on the same day as an adulticide.

Imidacloprid is toxic for birds, especially canaries.

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

Avoid contact with skin, eyes or mouth.
Do not eat, drink or smoke during application.
Wash hands thoroughly after use.

After application do not stroke or groom animals until the application site is dry.
In case of accidental spillage onto skin, wash off immediately with soap and water.
People with a known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In very rare cases the product may cause skin sensitisation or transient skin reactions (for example numbness, irritation or burning/tingling sensation).
In very rare cases the product may cause respiratory irritation in sensitive individuals.
If the product accidentally gets into eyes, they should be thoroughly flushed with water.
If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical advice immediately and show the package leaflet or label to the physician.

The solvent in Advocate may stain or damage 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)

Use of the product may result in transient pruritus in dogs. Vomiting can occur on rare occasions. Transient local skin sensitivity reactions including increased itching, hair loss, greasy fur and redness at application site have been reported in very rare cases in spontaneous (pharmacovigilance) reports. These signs disappear without further treatment. If the animal licks the application site after treatment, neurological signs (most of which are transient) may be observed in very rare cases (see section 4.10).

The product tastes bitter. 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. Correct application will minimise licking of the application sites.

The product may in very rare cases cause at the application site a sensation resulting in transient behavioural changes such as lethargy, agitation, and inappetence.

A field study has shown that in heartworm positive dogs with microfilaraemia there is a risk of severe respiratory signs (coughing, tachypnea and dyspnea) that may require prompt veterinary treatment. In the study these reactions were common (seen in 2 of 106 treated dogs). Gastrointestinal signs (vomiting, diarrhoea, inappetence) and lethargy are also common adverse reactions following treatment in such dogs.

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

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in the target species. Therefore, the use of the product is not recommended in animals intended for breeding or during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

During treatment with Advocate no other antiparasitic macrocyclic lactone should be administered.

No interactions between Advocate and routinely used veterinary medicinal products or medical or surgical procedures have been observed.

Safety of Advocate when administered on the same day as an adulticide to remove adult heartworms has not been evaluated.

4.9 Amounts to be administered and administration route

Dosage schedule:

The recommended minimum doses are 10 mg/kg bodyweight imidacloprid and 2.5 mg/kg bodyweight moxidectin, equivalent to 0.1 ml/kg bodyweight Advocate for dogs.

The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation.

Weight of dog [kg]	Pipette size to be used	Volume [ml]	Imidacloprid [mg/kg bw]	Moxidectin [mg/kg bw]
≤ 4 kg	Advocate for small dogs	0.4	minimum of 10	minimum of 2.5
> 4–10 kg	Advocate for medium dogs	1.0	10–25	2.5–6.25
> 10–25 kg	Advocate for large dogs	2.5	10–25	2.5–6.25
> 25–40 kg	Advocate for extra-large dogs	4.0	10–16	2.5–4
> 40 kg	the appropriate combination of pipettes			

Flea treatment and prevention (Ctenocephalides felis)

One treatment prevents future flea infestation for 4 weeks. Existing pupae in the environment may emerge for 6 weeks or longer after treatment is initiated, depending upon climatic conditions. Therefore, it may be necessary to combine Advocate treatment with environmental treatments aimed at breaking the flea life cycle in the surroundings. This can result in a more rapid reduction in the household flea population. The product should be administered at monthly intervals when used as part of a treatment strategy for flea allergy dermatitis.

Treatment of biting lice (Trichodectes canis)

A single dose should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment.

Treatment of ear mite infestation (Otodectes cynotis)

A single dose of the product should be administered. Loose debris should be gently removed from the external ear canal at each treatment. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment. Do not apply directly to the ear canal.

Treatment of sarcoptic mange (caused by Sarcoptes scabiei var. *canis)*

A single dose should be administered twice 4 weeks apart.

Treatment of demodicosis (caused by Demodex canis)

The administration of a single dose every 4 weeks for 2 to 4 months is efficacious against *Demodex canis* and leads to a marked improvement of clinical signs particularly in mild to moderate cases. Especially severe cases may require more prolonged and more frequent treatment. To achieve the best possible response in these severe cases, at the discretion of the veterinarian, Advocate can be applied once a week and for a prolonged time. In all cases it is essential that the treatment should be continued until skin scrapings are negative on at least 2 consecutive monthly occasions. Treatment should be stopped in dogs that show no improvement or do not respond in mite count after 2 months treatment. Alternative treatment should be administered. Seek the advice of your veterinarian.

As demodicosis is a multi-factorial disease, where possible, it is advisable to also treat any underlying disease appropriately.

Prevention of heartworm disease (D. immitis)

Dogs in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in section 4.5 should be considered.

For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit *D. immitis* larvae) are present. The product may be administered throughout the year. The first dose may be given after first possible exposure to mosquitoes, but not more than one month after this exposure. Treatment should continue at regular monthly intervals until 1 month after the last exposure to

mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with Advocate must be given within 1 month of the last dose of the former medication.

In non-endemic areas there should be no risk of dogs having heartworm. Therefore, they can be treated without special precautions.

Prevention of cutaneous dirofilariosis (skinworm) (D. repens)

For prevention of cutaneous dirofilariosis, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit *D. repens* larvae) are present. The product may be administered throughout the year or at least 1 month before the first expected exposure to mosquitoes. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month.

Treatment of microfilariae (D. immitis)

Advocate should be administered monthly for two consecutive months.

Treatment of cutaneous dirofilariosis (skin worm) (adult stages of Dirofilaria repens)

Advocate should be administered monthly for six consecutive months.

Reduction of microfilariae (skin worm) (D. repens)

The product should be administered monthly for four consecutive months.

Treatment and prevention of Angiostrongylus vasorum

A single dose should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment.
In endemic areas regular monthly applications will prevent angiostrongylosis and patent infection with *Angiostrongylus vasorum*.

Treatment of Crenosoma vulpis

A single dose should be administered.

Prevention of spirocercosis (Spirocerca lupi)

The product should be administered monthly.

Treatment of Eucoleus (syn. Capillaria) boehmi (adults)

The product should be administered monthly for two consecutive months. It is advisable to prevent auto-coprophagia between the two treatments in order to prevent possible reinfection.

Treatment of the eye worm Thelazia callipaeda (adults)

A single dose of the product should be administered.

Roundworm, hookworm and whipworm treatment (*Toxocara canis, Ancylostoma caninum, Uncinaria stenocephala*, T*oxascaris leonina* and *Trichuris vulpis*).

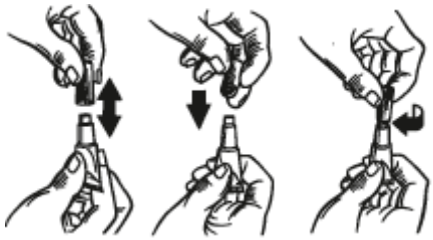
In areas endemic for heartworm, monthly treatment may significantly reduce the risk of re-infection caused by the respective round-, hook- and whipworms. In areas non-endemic for heartworm, the product can be used as part of a seasonal prevention programme against fleas and gastrointestinal nematodes.

Studies have shown that monthly treatment of dogs will prevent infections caused by *Uncinaria stenocephala.*

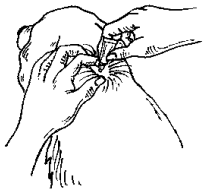
Method of administration

For external use only.

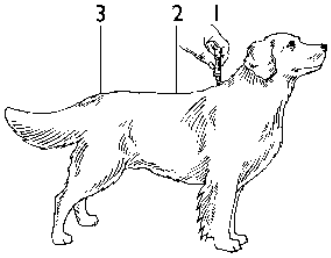
Remove one pipette from the package. Then hold the pipette in an upright position, and twist and pull off the cap. Reverse the cap and use it to twist and remove the seal from the pipette, as shown.



For dogs up to 25 kg:
With the dog in a standing position, part the coat between the shoulder blades until the skin is visible. Wherever possible apply to undamaged skin. Place the tip of the pipette on the skin and squeeze the pipette firmly several times to empty its contents directly onto the skin.



For dogs of more than 25 kg:
For easy application the dog should be standing. The entire contents of the pipette should be applied evenly as 3 or 4 spots along the top of the back, from between the shoulders to the base of the tail. At each spot, part the coat until the skin is visible. Wherever possible apply to undamaged skin. Place the tip of the pipette on the skin and gently squeeze the pipette to expel a portion of its contents directly onto the skin. Do not apply an excessive amount of solution at any one spot, as that could cause some of the product to run down the animal's side.



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

Up to 10 times the recommended dose was tolerated in adult dogs with no evidence of adverse effects or undesirable clinical signs. Five times the recommended minimum dose applied at weekly intervals for 17 weeks was investigated in dogs aged over 6 months and tolerated with no evidence of adverse effects or undesirable clinical signs.
The product was administered to puppies at up to 5 times the recommended dose, every 2 weeks for 6 treatments, and there were no serious safety concerns. Transient mydriasis, salivation, vomiting and transient rapid respiration were observed.
After accidental oral ingestion or overdose, neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur in very rare cases.
Ivermectin-sensitive Collie dogs tolerated up to 5 times the recommended dose repeated at monthly intervals without any adverse effects, but the safety of application at weekly intervals has not been investigated in ivermectin-sensitive Collie dogs. When 40% of the unit dose was given orally, severe neurological signs were observed. Oral administration of 10% of the recommended dose produced no adverse effects.
Dogs infected with adult heartworms tolerated up to 5 times the recommended dose, every 2 weeks for 3 treatments, without any adverse effects.

In case of accidental oral uptake, symptomatic treatment should be administered. There is no known specific antidote. The use of activated charcoal may be beneficial.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiparasitic products, insecticides and repellents, macrocyclic lactones, milbemycins.
ATCvet code: QP54AB52.

5.1 Pharmacodynamic properties

Imidacloprid, 1-(6-Chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Chemically, it is more accurately described as a chloronicotinyl nitroguanidine. Imidacloprid is effective against larval flea stages and adult fleas. Flea larvae in the pet's surroundings are killed after contact with a pet treated with the product. Imidacloprid has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) of the flea. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinergic receptors and the postulated poor penetration through the blood-brain barrier in mammals, it has virtually no effect on the mammalian CNS. Imidacloprid has minimal pharmacological activity in mammals.

Moxidectin, 23-(O-methyloxime)-F28249 alpha is a second-generation macrocyclic lactone of the milbemycin family. It is a parasiticide which is active against many internal and external parasites. Moxidectin is active against larval stages of *Dirofilaria immitis* (L1, L3, L4) and *Dirofilaria repens* (L1, L3). It is also active against gastrointestinal nematodes. Moxidectin interacts with GABA and glutamate-gated chloride channels. This leads to opening of the chloride channels on the postsynaptic junction, the inflow of chloride ions and induction of an irreversible resting state. The result is flaccid paralysis of affected parasites, followed by their death and/or expulsion.
The drug has a persistent action and protects dogs for 4 weeks after a single application against re-infection with the following parasites: *Dirofilaria immitis*, *Dirofilaria repens*, *Angiostrongylus vasorum*.

5.2 Pharmacokinetic particulars

After topical administration of the product, imidacloprid is rapidly distributed over the animal's skin within one day of application. It can be found on the body surface throughout the treatment interval. Moxidectin is absorbed through the skin, reaching maximum plasma concentrations approximately 4 to 9 days after treatment in dogs. Following absorption from the skin, moxidectin is distributed systemically throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. It is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month.
The T ½ in dogs is about 28.4 days.
Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in dogs.

Environmental properties

See sections 4.5 and 6.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Butylhydroxytoluene
Propylene carbonate

6.2 Major incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and composition of immediate packaging

Container material	White polypropylene unit dose pipette with screw cap.
Pack sizes	0.4 ml, 1.0 ml, 2.5 ml and 4.0 ml per pipette. Blister pack containing 1, 2, 3, 4, 6, 9, 12, 21 or 42 unit dose pipettes.

Not all pack sizes may be marketed.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
Advocate should not enter water courses as this may be dangerous for fish and other aquatic organisms.

7. MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH
51368 Leverkusen
GERMANY

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/005-012, EU/2/03/039/015-018, EU/2/03/039/023-030, EU/2/03/039/039-054

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02/04/2003.
Date of last renewal: 14/01/2013.

10. DATE OF REVISION OF THE TEXT

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

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONSREGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton, pack size of 1, 2, 3, 4, 6, 9, 12, 21 and 42 pipettes.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 40 mg + 4 mg spot-on solution for small cats and ferrets
Imidacloprid, moxidectin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 0.4 ml pipette contains:
Active substances: 40 mg imidacloprid, 4 mg moxidectin

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette
2 pipettes
3 pipettes
4 pipettes
6 pipettes
9 pipettes
12 pipettes
21 pipettes
42 pipettes

5. TARGET SPECIES

For small cats weighing 4 kg or less and ferrets

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

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

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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

Bayer Animal Health GmbH, 51368 Leverkusen, GERMANY

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/001	3 pipettes
EU/2/03/039/002	6 pipettes
EU/2/03/039/013	4 pipettes
EU/2/03/039/019	21 pipettes
EU/2/03/039/020	42 pipettes
EU/2/03/039/031	1 pipette
EU/2/03/039/032	2 pipettes
EU/2/03/039/033	9 pipettes
EU/2/03/039/034	12 pipettes

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton, pack size of 1, 2, 3, 4, 6, 9, 12, 21 and 42 pipettes

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 80 mg + 8 mg spot-on solution for large cats
Imidacloprid, moxidectin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 0.8 ml pipette contains:
Active substances: 80 mg imidacloprid, 8 mg moxidectin

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette
2 pipettes
3 pipettes
4 pipettes
6 pipettes
9 pipettes
12 pipettes
21 pipettes
42 pipettes

5. TARGET SPECIES

For large cats weighing between 4 kg and 8 kg.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

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

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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

Bayer Animal Health GmbH, 51368 Leverkusen, GERMANY.

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/003	3 pipettes
EU/2/03/039/004	6 pipettes
EU/2/03/039/014	4 pipettes
EU/2/03/039/021	21 pipettes
EU/2/03/039/022	42 pipettes
EU/2/03/039/035	1 pipette
EU/2/03/039/036	2 pipettes
EU/2/03/039/037	9 pipettes
EU/2/03/039/038	12 pipettes

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton, pack size of 1, 2, 3, 4, 6, 9, 12, 21 and 42 pipettes

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 40 mg + 10 mg spot-on solution for small dogs
Imidacloprid, moxidectin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 0.4 ml pipette contains:
Active substances: 40 mg imidacloprid, 10 mg moxidectin.

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette
2 pipettes
3 pipettes
4 pipettes
6 pipettes
9 pipettes
12 pipettes
21 pipettes
42 pipettes

5. TARGET SPECIES

For small dogs weighing 4 kg or less.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

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

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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

Bayer Animal Health GmbH, 51368 Leverkusen, GERMANY.

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/005	3 pipettes
EU/2/03/039/006	6 pipettes
EU/2/03/039/015	4 pipettes
EU/2/03/039/023	21 pipettes
EU/2/03/039/024	42 pipettes
EU/2/03/039/039	1 pipette
EU/2/03/039/040	2 pipettes
EU/2/03/039/041	9 pipettes
EU/2/03/039/042	12 pipettes

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton, pack size of 1, 2, 3, 4, 6, 9, 12, 21 and 42 pipettes

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 100 mg + 25 mg spot-on solution for medium dogs
Imidacloprid, moxidectin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 1 ml pipette contains:
Active substances: 100 mg imidacloprid, 25 mg moxidectin.

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette
2 pipettes
3 pipettes
4 pipettes
6 pipettes
9 pipettes
12 pipettes
21 pipettes
42 pipettes

5. TARGET SPECIES

For medium dogs weighing between 4 kg and 10 kg.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

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

8. WITHDRAWAL PERIOD(S)

Not applicable

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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

Bayer Animal Health GmbH, 51368 Leverkusen, GERMANY.

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/007	3 pipettes
EU/2/03/039/008	6 pipettes
EU/2/03/039/016	4 pipettes
EU/2/03/039/025	21 pipettes
EU/2/03/039/026	42 pipettes
EU/2/03/039/043	1 pipette
EU/2/03/039/044	2 pipettes
EU/2/03/039/045	9 pipettes
EU/2/03/039/046	12 pipettes

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton, pack size of 1, 2, 3, 4, 6, 9, 12, 21 and 42 pipettes

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 250 mg + 62.5 mg spot-on solution for large dogs
Imidacloprid, moxidectin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 2.5 ml pipette contains:
Active substances: 250 mg imidacloprid, 62.5 mg moxidectin.

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette
2 pipettes
3 pipettes
4 pipettes
6 pipettes
9 pipettes
12 pipettes
21 pipettes
42 pipettes

5. TARGET SPECIES

For large dogs weighing between 10 kg and 25 kg.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

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

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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

Bayer Animal Health GmbH, 51368 Leverkusen, GERMANY.

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/009	3 pipettes
EU/2/03/039/010	6 pipettes
EU/2/03/039/017	4 pipettes
EU/2/03/039/027	21 pipettes
EU/2/03/039/028	42 pipettes
EU/2/03/039/047	1 pipette
EU/2/03/039/048	2 pipettes
EU/2/03/039/049	9 pipettes
EU/2/03/039/050	12 pipettes

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton, pack size of 1, 2, 3, 4, 6, 9, 12, 21 and 42 pipettes.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 400 mg + 100 mg spot-on solution for extra-large dogs
Imidacloprid, moxidectin

2. STATEMENT OF ACTIVE SUBSTANCES

Each 4 ml pipette contains:
Active substances: 400 mg imidacloprid, 100 mg moxidectin.

3. PHARMACEUTICAL FORM

Spot-on solution

4. PACKAGE SIZE

1 pipette
2 pipettes
3 pipettes
4 pipettes
6 pipettes
9 pipettes
12 pipettes
21 pipettes
42 pipettes

5. TARGET SPECIES

For extra-large dogs weighing between 25 kg and 40 kg.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

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

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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

Bayer Animal Health GmbH, 51368 Leverkusen, GERMANY.

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/03/039/011	3 pipettes
EU/2/03/039/012	6 pipettes
EU/2/03/039/018	4 pipettes
EU/2/03/039/029	21 pipettes
EU/2/03/039/030	42 pipettes
EU/2/03/039/051	1 pipette
EU/2/03/039/052	2 pipettes
EU/2/03/039/053	9 pipettes
EU/2/03/039/054	12 pipettes

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Advocate for small cats and ferrets
Pipette

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate

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

0.4 ml

3. ROUTE(S) OF ADMINISTRATION

Spot-on

4. BATCH NUMBER

Lot {number}

5. EXPIRY DATE

EXP {month/year}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Advocate for large cats
Pipette

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate

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

0.8 ml

3. ROUTE(S) OF ADMINISTRATION

Spot-on

4. BATCH NUMBER

Lot {number}

5. EXPIRY DATE

EXP {month/year}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Advocate for small dogs
Pipette

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate

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

0.4 ml

3. ROUTE(S) OF ADMINISTRATION

Spot-on

4. BATCH NUMBER

Lot {number}

5. EXPIRY DATE

EXP {month/year}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Advocate for medium dogs
Pipette

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate

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

1 ml

3. ROUTE(S) OF ADMINISTRATION

Spot-on

4. BATCH NUMBER

Lot {number}

5. EXPIRY DATE

EXP {month/year}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Advocate for large dogs
Pipette

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate

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

2.5 ml

3. ROUTE(S) OF ADMINISTRATION

Spot-on

4. BATCH NUMBER

Lot {number}

5. EXPIRY DATE

EXP {month/year}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Advocate for extra-large dogs
Pipette

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate

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

4 ml

3. ROUTE(S) OF ADMINISTRATION

Spot-on

4. BATCH NUMBER

Lot {number}

5. EXPIRY DATE

EXP {month/year}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate for small cats and ferrets
(≤ 4 kg)

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

0.4 ml

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH

4. EXPIRY DATE

EXP {month/year}

5. BATCH NUMBER

Lot {number}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate for large cats

(> 4–8 kg)

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

0.8 ml

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH

4. EXPIRY DATE

EXP {month/year}

5. BATCH NUMBER

Lot {number}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate for small dogs

(≤ 4 kg)

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

0.4 ml

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH

4. EXPIRY DATE

EXP {month/year}

5. BATCH NUMBER

Lot {number}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate for medium dogs

(> 4–10 kg)

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

1 ml

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH

4. EXPIRY DATE

EXP {month/year}

5. BATCH NUMBER

Lot {number}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate for large dogs

(> 10–25 kg)

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

2.5 ml

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH

4. EXPIRY DATE

EXP {month/year}

5. BATCH NUMBER

Lot {number}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate for extra-large dogs

(> 25–40 kg)

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

4 ml

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Animal Health GmbH

4. EXPIRY DATE

EXP {month/year}

5. BATCH NUMBER

Lot {number}

6. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Advocate 40 mg + 4 mg spot-on solution for small cats and ferrets
Advocate 80 mg + 8 mg spot-on solution for large cats

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

Marketing authorisation holder:
Bayer Animal Health GmbH
51368 Leverkusen
GERMANY

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

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 40 mg + 4 mg spot-on solution for small cats and ferrets
Advocate 80 mg + 8 mg spot-on solution for large cats
Imidacloprid, moxidectin

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

Each unit dose pipette contains:

	Unit dose	Imidacloprid	Moxidectin
Advocate for small cats (≤ 4 kg) and ferrets	0.4 ml	40 mg	4 mg
Advocate for large cats (> 4–8 kg)	0.8 ml	80 mg	8 mg

Excipients: Benzyl alcohol, 1 mg/ml butylhydroxytoluene (E 321; as antioxidant).

Clear yellow to brownish solution.

4. INDICATION(S)

For cats suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of ear mite infestation (*Otodectes cynotis*),
- the treatment of notoedric mange (*Notoedres cati*),
- the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) (adults),
- the prevention of lungworm disease (L3/L4 larvae of *Aelurostrongylus abstrusus*),
- the treatment of the lungworm *Aelurostrongylus abstrusus* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* (roundworm) and *Ancylostoma tubaeforme* (hookworm).

The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

For ferrets suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*).

5. CONTRAINDICATIONS

Do not use in kittens under 9 weeks of age.

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

For ferrets:
Do not use Advocate for large cats (0.8 ml) or Advocate for dogs (any size).

For dogs, the corresponding "Advocate for dog" product, which contains 100 mg/ml imidacloprid and 25 mg/ml moxidectin, must be used.

Do not use on canaries.

6. ADVERSE REACTIONS

Use of the product may result in transient pruritus in cats. On rare occasions greasy fur, erythema and vomiting can occur. These signs disappear without further treatment. The product may, in rare cases, cause local hypersensitivity reactions. If the animal licks the application site after treatment, neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may be observed in very rare cases.

The product tastes bitter. 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. Correct application will minimise licking of the application site.

The product may in very rare cases cause at the application site a sensation resulting in transient behavioural changes such as lethargy, agitation, and inappetence.

In case of accidental oral uptake, symptomatic treatment should be performed by a veterinary surgeon. There is no known specific antidote. The use of activated charcoal may be beneficial.

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, ferrets

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

For external use only.

To prevent licking, apply topically to the skin restricting the area of application to the animal's neck at the base of the skull.

Dosage schedule for cats:

The recommended minimum doses are 10 mg/kg bodyweight imidacloprid and 1.0 mg/kg bodyweight moxidectin, equivalent to 0.1 ml/kg bodyweight Advocate for cats.

The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation.

Weight of cat [kg]	Pipette size to be used	Volume [ml]	Imidacloprid [mg/kg bw]	Moxidectin [mg/kg bw]
≤ 4 kg	Advocate for small cats	0.4	minimum of 10	minimum of 1
> 4–8 kg	Advocate for large cats	0.8	10–20	1–2
> 8 kg	appropriate combination of pipettes			

Flea treatment and prevention (*Ctenocephalides felis*)

One treatment prevents further flea infestation for 4 weeks. Pre-existing pupae in the environment may continue to emerge for 6 weeks or longer after treatment is initiated depending upon climatic conditions. Therefore, it may be necessary to combine Advocate treatment with treatments aimed at breaking the flea life cycle in the surroundings. This can result in more rapid reductions in the household flea population. The product should be administered at monthly intervals when used as part of a treatment strategy for flea allergy dermatitis.

Treatment of ear mite infestation (Otodectes cynotis)

A single dose of the product should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment. Do not apply directly to the ear canal.

Treatment of notoedric mange (Notoedres cati)

A single dose of the product should be administered.

Treatment of the lungworm Eucoleus aerophilus (syn. Capillaria aerophila)(adults)

A single dose of the product should be administered.

Prevention of Aelurostrongylus abstrusus

The product should be administered monthly.

Treatment of Aelurostrongylus abstrusus

Advocate should be administered monthly for three consecutive months.

Treatment of the eye worm Thelazia callipaeda (adults)

A single dose of the product should be administered.

Heartworm prevention (Dirofilaria immitis)

Cats in endemic areas, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in the section "SPECIAL WARNING(S)" should be considered.

For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit heartworm larvae) are present. The product may be administered throughout the year. The first dose may be given after first possible exposure to mosquitoes, but not more than one month after this exposure. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with Advocate must be given within 1 month of the last dose of the former medication.

In non-endemic areas there should be no risk of cats having heartworm. Therefore, they can be treated without special considerations.

Roundworm and hookworm treatment (Toxocara cati and Ancylostoma tubaeforme).

In areas endemic for heartworm, monthly treatment may significantly reduce the risk of re-infection caused by the respective roundworms and hookworms. In areas non-endemic for heartworm, the product can be used as part of a seasonal prevention programme against fleas and gastrointestinal nematodes.

Dosage schedule for ferrets:

One pipette of Advocate spot-on solution for small cats (0.4 ml) should be administered per animal. Do not exceed the recommended dose.
The treatment schedule should be based on the local epidemiological situation.

Flea treatment and prevention (Ctenocephalides felis)

One treatment prevents future flea infestation for 3 weeks. Under heavy flea pressure it may be necessary to repeat administration after 2 weeks.

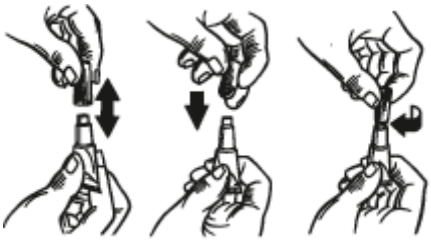
Heartworm prevention (Dirofilaria immitis)

Ferrets in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in the section "SPECIAL WARNING(S)" should be considered.

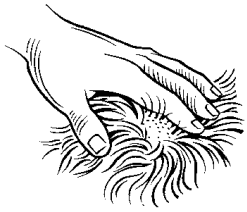
For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit heartworm larvae) are present. The product may be administered throughout the year. The first dose may be given after first possible exposure to mosquitoes, but not more than one month after this exposure. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes.
In non-endemic areas there should be no risk of ferrets having heartworm. Therefore, they can be treated without special precautions.

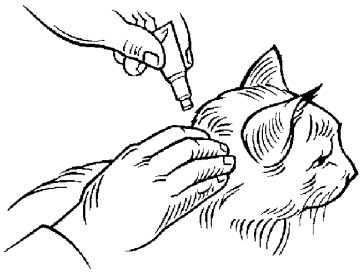
9. ADVICE ON CORRECT ADMINISTRATION

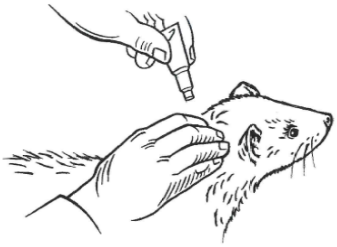
Remove one pipette from the package. Then hold the pipette in an upright position, and twist and pull off cap. Reverse the cap and use it to twist and remove the seal from the pipette, as shown.



Part the fur on the animal's neck at the base of the skull until the skin is visible. Place the tip of the pipette on the skin and squeeze the pipette firmly several times to empty its contents directly onto the skin. Application at the base of the skull will minimise the opportunity for the animal to lick the product. Apply only to undamaged skin.







10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 30 °C.
Do not use this veterinary medicinal product after the expiry date stated on the label and carton. The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

Special warnings for each target species:
The product’s efficacy has not been tested in ferrets weighing over 2 kg and therefore the duration of effect might be shorter in these animals.

Brief contact of the animal with water on one or two occasions between monthly treatments is unlikely to significantly reduce the efficacy of the product. However, frequent shampooing or immersion of the animal in water after treatment may reduce the efficacy of the product.

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance. The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see also sections 4 and 8).

Special precautions for use in animals:
Treatment of cats weighing less than 1 kg and ferrets weighing less than 0.8 kg should be based on a benefit-risk assessment.

There is limited experience on the use of the product in sick and debilitated animals, thus the product should only be used based on a benefit-risk assessment for these animals.

Do not apply in the mouth, in the eyes or the ears of the animal.

Care should be taken that the product is not ingested by animals and does not come into contact with the eyes or mouth of the recipient and/or other animals. Consider carefully the correct application method described in section 9, especially that the product should be applied to the site specified in order to minimise the risk for the animal to lick the product. Do not allow recently treated animals to groom each other. Do not allow treated animals to come into contact with untreated animals until the application site is dry.

It is recommended that cats and ferrets living in, or travelling to, areas endemic for heartworm are treated monthly with the product to protect them from heartworm disease.

Whilst the accuracy of diagnosis of heartworm infection is limited, it is recommended that attempts be made to check the heartworm status of any cat and ferret aged over 6 months, prior to beginning of prophylactic treatment, as use of the product on cats or ferrets which have adult heartworm may cause serious adverse effects, including death. If adult heartworm infection is diagnosed, the infection should be treated in accordance with current scientific knowledge.

In certain individual cats *Notoedres cati* infestation may be severe. In these severe cases concomitant supportive treatment is necessary as treatment with the product alone may not be sufficient to prevent death of the animal.

Imidacloprid is toxic for birds, especially canaries.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Avoid contact with skin, eyes or mouth.
Do not eat, drink or smoke during application.
Wash hands thoroughly after use.
After application do not stroke or groom animals until the application site is dry.
In case of accidental spillage onto skin, wash off immediately with soap and water.
People with a known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In very rare cases the product may cause skin sensitisation or transient skin reactions (for example numbness, irritation or burning/tingling sensation).
In very rare case the product may cause respiratory irritation in sensitive individuals.
If the product accidentally gets into eyes, they should be thoroughly flushed with water.
If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical advice immediately and show the package leaflet or the label to the physician.

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

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation in the target species. Therefore, the use of the product is not recommended in animals intended for breeding or during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:
During treatment with Advocate no other antiparasitic macrocyclic lactone should be administered.

No interactions between Advocate and routinely used veterinary medicinal products or medical or surgical procedures have been observed.

Overdose (symptoms, emergency procedures, antidotes):
Up to 10 times the recommended dose was tolerated in cats with no evidence of adverse effects or undesirable clinical signs.
The product was administered to kittens at up to 5 times the recommended dose, every 2 weeks for 6 treatments, and there were no serious safety concerns. Transient mydriasis, salivation, vomiting and transient rapid respiration were observed.
After accidental oral ingestion or overdose, neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur in very rare cases.

The product was administered to ferrets at 5 times the recommended dose, every 2 weeks for 4 treatments, and there was no evidence of adverse effects or undesirable clinical signs.

In case of accidental oral uptake, symptomatic treatment should be administered. There is no known specific antidote. The use of activated charcoal may be beneficial.

Incompatibilities:
None known.

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

Medicines should not be disposed of via wastewater or household waste. Advocate should not enter water courses as this may be dangerous for fish and other aquatic organisms.
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

Imidacloprid is effective against larval flea stages and adult fleas. Flea larvae in the pet's surroundings are killed after contact with a pet treated with the product.

The product has a persistent action and protects cats for 4 weeks after a single application against reinfection with *Dirofilaria immitis*.
Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in cats.

Pack sizes: 0.4 ml and 0.8 ml per pipette; blister packs containing 1, 2, 3, 4, 6, 9, 12, 21 or 42 unit dose pipettes.

Not all pack sizes may be marketed.

PACKAGE LEAFLET:
Advocate 40 mg + 10 mg spot-on solution for small dogs
Advocate 100 mg + 25 mg spot-on solution for medium dogs
Advocate 250 mg + 62.5 mg spot-on solution for large dogs
Advocate 400 mg + 100 mg spot-on solution for extra-large 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:
Bayer Animal Health GmbH
51368 Leverkusen
GERMANY

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

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Advocate 40 mg + 10 mg spot-on solution for small dogs
Advocate 100 mg + 25 mg spot-on solution for medium dogs
Advocate 250 mg + 62.5 mg spot-on solution for large dogs
Advocate 400 mg + 100 mg spot-on solution for extra-large dogs
Imidacloprid, moxidectin

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

Each unit dose pipette contains:

	Unit Dose	Imidacloprid	Moxidectin
Advocate for small dogs (≤ 4 kg)	0.4 ml	40 mg	10 mg
Advocate for medium dogs (> 4–10 kg)	1.0 ml	100 mg	25 mg
Advocate for large dogs (> 10–25 kg)	2.5 ml	250 mg	62.5 mg
Advocate for extra-large dogs (> 25–40 kg)	4.0 ml	400 mg	100 mg

Excipients: Benzyl alcohol, 1 mg/ml butylhydroxytoluene (E 321; as antioxidant).

Clear yellow to brownish solution.

4. INDICATION(S)

For dogs suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of biting lice (*Trichodectes canis*),
- the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of circulating microfilariae (*Dirofilaria immitis*),
- the treatment of cutaneous dirofilariosis (skinworm) (adult stages of *Dirofilaria repens*)
- the prevention of cutaneous dirofilariosis (skinworm) (L3 larvae of *Dirofilaria repens*),

- the reduction of circulating microfilariae (*Dirofilaria repens*),
- the prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*),
- the treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis,*
- the prevention of spirocercosis (*Spirocerca lupi*),
- the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara canis* (roundworm)*, Ancylostoma caninum* (hookworm) and *Uncinaria stenocephala* (hookworm), adults of *Toxascaris leonina* (roundworm) and *Trichuris vulpis* (whipworm)).

The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

5. CONTRAINDICATIONS

Do not use in puppies under 7 weeks of age.

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

Do not use in dogs classified as Class 4 for heartworm disease as the safety of the product has not been evaluated in this animal group.

For cats, the corresponding “Advocate for cat” product, which contains 100 mg/ml imidacloprid and 10 mg/ml moxidectin, must be used.

For ferrets:
Do not use Advocate for dogs. Only “Advocate for small cats and ferrets” (0.4 ml) must be used.

Do not use on canaries.

6. ADVERSE REACTIONS

Use of the product may result in transient pruritus in dogs. Transient local skin sensitivity reactions including increased itching, hair loss, greasy fur and redness at application site have been reported in very rare cases in spontaneous (pharmacovigilance) reports. Vomiting can occur on rare occasions. These signs disappear without further treatment. If the animal licks the application site after treatment, neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may be observed in very rare cases.

The product tastes bitter. 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. Correct application will minimise licking of the application sites.

The product may in very rare cases cause at the application site a sensation resulting in transient behavioural changes such as lethargy, agitation, and inappetence.

A field study has shown that in heartworm positive dogs with microfilaraemia there is a risk of severe respiratory signs (coughing, tachypnea and dyspnea) that may require prompt veterinary treatment. In the study these reactions were common (seen in 2 of 106 treated dogs). Gastrointestinal signs (vomiting, diarrhoea, inappetence) and lethargy are also common adverse reactions following treatment in such dogs.

In case of accidental oral uptake, symptomatic treatment should be administered by a veterinary surgeon. There is no known specific antidote. The use of activated charcoal may be beneficial.

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

Dogs

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

For external use only.

Apply topically to the skin between the shoulder blades.

Dosage schedule

The recommended minimum doses are 10 mg/kg bodyweight imidacloprid and 2.5 mg/kg bodyweight moxidectin, equivalent to 0.1 ml/kg bodyweight Advocate for dogs.

The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation.

Weight of dog [kg]	Pipette size to be used	Volume [ml]	Imidacloprid [mg/kg bw]	Moxidectin [mg/kg bw]
≤ 4 kg	Advocate for small dogs	0.4	minimum of 10	minimum of 2.5
> 4–10 kg	Advocate for medium dogs	1.0	10–25	2.5–6.25
> 10–25 kg	Advocate for large dogs	2.5	10–25	2.5–6.25
> 25–40 kg	Advocate for extra-large dogs	4.0	10–16	2.5–4
> 40 kg	appropriate combination of pipettes			

Flea treatment and prevention (Ctenocephalides felis)

One treatment prevents further flea infestation for 4 weeks. Pre-existing pupae in the environment may continue to emerge for 6 weeks or longer after treatment is initiated depending upon climatic conditions. Therefore, it may be necessary to combine Advocate treatment with treatments aimed at breaking the flea life cycle in the surroundings. This can result in more rapid reductions in the household flea population. The product should be administered at monthly intervals when used as part of a treatment strategy for flea allergy dermatitis.

Treatment of biting lice (Trichodectes canis)

A single dose should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment.

Treatment of ear mite infestation (Otodectes cynotis)

A single dose of the product should be administered. Loose debris should be gently removed from the external ear canal at each treatment. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment. Do not apply directly to the ear canal.

Treatment of sarcoptic mange (caused by Sarcoptes scabiei var. *canis)*

A single dose should be administered twice 4 weeks apart.

Treatment of demodicosis (caused by Demodex canis)

The administration of a single dose every 4 weeks for 2 to 4 months is efficacious against *Demodex canis* and leads to a marked improvement of clinical signs particularly in mild to moderate cases. Especially severe cases may require more prolonged and more frequent treatment. To achieve the best possible response in these severe cases, at the discretion of the veterinarian, Advocate can be applied once a week and for a prolonged time. In all cases it is essential that the treatment should be continued until skin scrapings are negative on at least 2 consecutive monthly occasions. Treatment should be stopped in dogs that show no improvement or do not respond in mite count after 2 months treatment. Alternative treatment should be administered. Seek the advice of your veterinarian.

As demodicosis is a multi-factorial disease, where possible, it is advisable to also treat any underlying disease appropriately.

Prevention of heartworm disease (D. immitis)

Dogs in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in the section "SPECIAL WARNING(S)" should be considered.

For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit *D. immitis* larvae) are present. The product may be administered throughout the year. The first dose may be given after first possible exposure to mosquitoes, but not more than one month after this exposure. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with Advocate must be given within 1 month of the last dose of the former medication.

In non-endemic areas there should be no risk of dogs having heartworm. Therefore, they can be treated without special precautions.

Pr*evention of cutaneous dirofilariosis (skinworm) (D. repens)*

For prevention of cutaneous dirofilariosis, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit *D. repens* larvae) are present. The product may be administered throughout the year or at least 1 month before the first expected exposure to mosquitoes. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month.

Treatment of microfilariae (D. immitis)

Advocate should be administered monthly for two consecutive months.

Treatment of cutaneous dirofilariosis (skin worm) (adult stages of Dirofilaria repens)

Advocate should be administered monthly for six consecutive months.

Reduction of microfilariae (skinworm) (D. repens)

The product should be administered monthly for four consecutive months.

Treatment and prevention of Angiostrongylus vasorum

A single dose should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment.
In endemic areas regular monthly application will prevent angiostrongylosis and patent infection with *Angiostrongylus vasorum*.

Treatment of Crenosoma vulpis

A single dose should be administered.

Prevention of spirocercosis (Spirocerca lupi)

The product should be administered monthly.

Treatment of Eucoleus (syn. Capillaria) boehmi (adults)

The product should be administered monthly for two consecutive months. It is advisable to prevent auto-coprophagia between the two treatments in order to prevent possible reinfection.

Treatment of the eye worm Thelazia callipaeda (adults)

A single dose of the product should be administered.

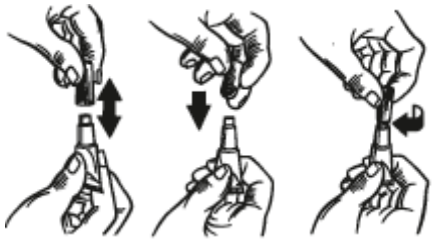
Roundworm, hookworm and whipworm treatment (Toxocara canis, Ancylostoma caninum, Uncinaria stenocephala, Toxascaris leonina and Trichuris vulpis).

In areas endemic for heartworm, monthly treatment may significantly reduce the risk of re-infection caused by the respective roundworm, hookworms and whipworms. In areas non-endemic for heartworm, the product can be used as part of a seasonal prevention programme against fleas and gastrointestinal nematodes.

Studies have shown that monthly treatment of dogs will prevent infections caused by *Uncinaria stenocephala.*

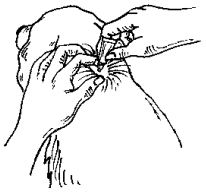
9. ADVICE ON CORRECT ADMINISTRATION

Remove one pipette from the package. Then hold the pipette in an upright position, and twist and pull off the cap. Reverse the cap and use it to twist and remove the seal from the pipette, as shown.

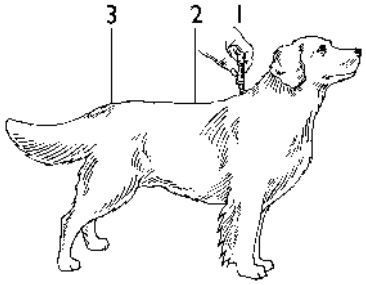


For dogs up to 25 kg:

With the dog in a standing position, part the coat between the shoulder blades until the skin is visible. Wherever possible apply to undamaged skin. Place the tip of the pipette on the skin and squeeze the pipette firmly several times to empty its contents directly onto the skin.



For dogs of more than 25 kg:
For easy application the dog should be standing. The entire contents of the pipette should be applied evenly as 3 or 4 spots along the top of the back, from between the shoulders to the base of the tail. At each spot part the coat until the skin is visible. Wherever possible apply to undamaged skin. Place the tip of the pipette on the skin and gently squeeze the pipette to expel a portion of its contents directly onto the skin. Do not apply an excessive amount of solution at any one spot, as that could cause some of the product to run down the animal's side.



10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 30 °C.
Do not use this veterinary medicinal product after the expiry date stated on the label and carton. The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

Special warning for each target species:
Brief contact of the animal with water on one or two occasions between monthly treatments is unlikely to significantly reduce the efficacy of the product. However, frequent shampooing or immersion of the animal in water after treatment may reduce the efficacy of the product.

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see also sections 4 and 8).

Efficacy against adult *Dirofilaria repens* has not been tested under field conditions.

Special precautions for use in animals:
Treatment of animals weighing less than 1 kg should be based on a benefit-risk assessment.

There is limited experience on the use of the product in sick and debilitated animals, thus the product should only be used based on a benefit-risk assessment for these animals.

Do not apply in the mouth, in the eyes or the ears of the animal.

Care should be taken that the product is not ingested by animals and does not come into contact with the eyes or mouth of the recipient and/or other animals. Consider carefully the correct application method described in section 9, especially that the product should be applied to the site specified in order to minimise the risk for the animal to lick the product. Do not allow recently treated animals to groom each other. Do not allow treated animals to come into contact with untreated animals until the application site is dry. When the product is applied in 3 to 4 separate spots, specific care should be taken to prevent the animal licking the application sites.

This product contains moxidectin (a macrocyclic lactone), therefore special care should be taken with Collie or Old English Sheep dogs and related breeds or crossbreeds, to correctly administer the product as described under the section "ADVICE ON CORRECT ADMINISTRATION"; in particular, oral uptake by Collie or Old English Sheep dogs and related breeds or crossbreeds should be prevented.

Advocate should not enter water courses as this may be dangerous for fish and other aquatic organism: moxidectin is highly toxic to aquatic organisms. Dogs should not be allowed to swim in surface waters for 4 days after treatment.

The safety of the product has only been evaluated in dogs classified as either Class 1 or 2 for heartworm disease in laboratory studies and in a few Class 3 dogs in a field study. Therefore, the use in dogs with obvious or severe symptoms of the disease should be based on a careful benefit-risk assessment by the treating veterinarian.

Although experimental overdosage studies have shown that the product may be safely administered to dogs infected with adult heartworms, it has no therapeutic efficacy against adult *Dirofilaria immitis*. It is therefore recommended that all dogs 6 months of age or more, living in areas endemic for heartworm, should be tested for existing adult heartworm infection before being treated with the product. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of Advocate has not been evaluated when administered on the same day as an adulticide.

Imidacloprid is toxic for birds, especially canaries.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Avoid contact with skin, eyes or mouth.
Do not eat, drink or smoke during application.
Wash hands thoroughly after use.
After application do not stroke or groom animals until the application site is dry.
In case of accidental spillage onto skin, wash off immediately with soap and water.
People with a known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In very rare cases the product may cause skin sensitisation or transient skin reactions (for example numbness, irritation or burning/tingling sensation).
In very rare cases the product may cause respiratory irritation in sensitive individuals.

If the product accidentally gets into eyes, they should be thoroughly flushed with water.
If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical advice immediately and show the package leaflet or label to the physician.

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

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation in the target species. Therefore, the use of the product is not recommended in animals intended for breeding or during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:
During treatment with Advocate no other antiparasitic macrocyclic lactone should be administered.

No interactions between Advocate and routinely used veterinary medicinal products or medical or surgical procedures have been observed.

Safety of Advocate when administered on the same day as an adulticide to remove adult heartworms has not been evaluated.

Overdose (symptoms, emergency procedures, antidotes):
Up to 10 times the recommended dose was tolerated in adult dogs with no evidence of adverse effects or undesirable clinical signs. Five times the recommended minimum dose applied at weekly intervals for 17 weeks was investigated in dogs aged over 6 months and tolerated with no evidence of adverse effects or undesirable clinical signs.
The product was administered to puppies at up to 5 times the recommended dose, every 2 weeks for 6 treatments, and there were no serious safety concerns. Transient mydriasis, salivation, vomiting and transient rapid respiration were observed.
After accidental oral ingestion or overdose, neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur in very rare cases.
Ivermectin-sensitive Collie dogs tolerated up to 5 times the recommended dose repeated at monthly intervals without any adverse effects, but the safety of application at weekly intervals has not been investigated in ivermectin-sensitive Collie dogs. When 40 % of the unit dose was given orally, severe neurological signs were observed. Oral administration of 10 % of the recommended dose produced no adverse effects.
Dogs infected with adult heartworms tolerated up to 5 times the recommended dose, every 2 weeks for 3 treatments, without any adverse effects.

In case of accidental oral uptake, symptomatic treatment should be administered. There is no known specific antidote. The use of activated charcoal may be beneficial.

Incompatibilities:
None known.

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

Medicines should not be disposed of via wastewater or household waste. Advocate should not enter water courses as this may be dangerous for fish and other aquatic organisms.
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

Imidacloprid is effective against larval flea stages and adult fleas. Flea larvae in the pet's surroundings are killed after contact with a pet treated with the product.

The drug has a persistent action and protects dogs for 4 weeks after a single application against re-infection with the following parasites: *Dirofilaria immitis*, *Dirofilaria repens*, *Angiostrongylus vasorum*.
Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in dogs.

Pack sizes: 0.4 ml, 1.0 ml, 2.5 ml and 4.0 ml per pipette; blister packs containing 1, 2, 3, 4, 6, 9, 12, 21 or 42 unit dose pipettes.

Not all pack sizes may be marketed.