Annex I

List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, marketing authorisation holder in the Member States

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Bayer Austria Ges.m.b.H Herbstraße 6-10 A-1160 Wien, Austria	Seresto 1,25 g + 0,56 g Halsband für Katzen und Hunde ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Austria	Bayer Austria Ges.m.b.H Herbstraße 6-10 A-1160 Wien, Austria	Seresto 1,25 g + 0,56 g Halsband für Hunde ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Austria	Bayer Austria Ges.m.b.H Herbstraße 6-10 A-1160 Wien, Austria	Seresto 4,50 g + 2,03 g Halsband für Hunde >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Belgium	Bayer SA-NV, J.E. Mommaertslaan 14 1831 Diegem (Machelen), Belgium	Seresto 1,25 g + 0,56 g halsband voor katten en honden ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Belgium	Bayer SA-NV, J.E. Mommaertslaan 14 1831 Diegem (Machelen), Belgium	Seresto 1,25 g + 0,56 g Halsband voor honden ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Belgium	Bayer SA-NV, J.E. Mommaertslaan 14 1831 Diegem (Machelen), Belgium	Seresto 4,50 g + 2,03 g halsband voor honden >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Bulgaria	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Форесто 1,25 g + 0,56 g, противопаразитна каишка за котки и кучета ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Bulgaria	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Форесто 4,50 g + 2,03 g, противопаразитна каишка за кучета >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Cyprus	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto 1.25 g + 0.56 g, περιλαίμιο για γάτες και σκύλους ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Cyprus	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto 1.25 g + 0.56 g, περιλαίμιο για σκύλους ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Cyprus	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto 4,50 g + 2,03 g, περιλαίμιο για σκύλους >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Czech Republic	Bayer s.r.o., Siemensova 2717/4, 155 80 Praha 5, Czech Republic	Foresto 1,25 + 0,56 obojek pro kocky a psy ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Czech Republic	Bayer s.r.o., Siemensova 2717/4, 155 80 Praha 5, Czech Republic	Foresto 4,5 + 2,03 obojek pro psy >8kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Denmark	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 1,25 g / 0,56 g halsbånd til katte og hunde ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Denmark	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet 1,25 g / 0,56 g halsbånd til hunde ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Denmark	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 4,5 g / 2,03 g halsbånd til hunde >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Estonia	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 1.25 g + 0.56 g ravimkaelarihm kassidele ja koertele ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Estonia	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 4.50 g + 2.03 g ravimkaelarihm koertele >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Finland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 1,25/0,56 g panta kissoille ja koirille alle 8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Finland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 1,25/0,56 g panta koirille alle 8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Finland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 4,5/2,03 g panta koirille yli 8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
France	Bayer Healthcare, 220 Avenue de la Recherche 59120, Loos, France	Seresto collier petits chiens	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
France	Bayer Healthcare, 220 Avenue de la Recherche 59120, Loos, France	Seresto collier grands chiens	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Germany	Bayer Vital GmbH, Geschäftsbereich Tiergesundheit 51368 Leverkusen Germany	Seresto 1,25 g + 0,56 g Halsband für Katzen und Hunde ≤8kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Germany	Bayer Vital GmbH, Geschäftsbereich Tiergesundheit 51368 Leverkusen Germany	Seresto 1,25 g + 0,56 g Halsband für Hunde ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Bayer Vital GmbH, Geschäftsbereich Tiergesundheit 51368 Leverkusen Germany	Seresto 4.50 g + 2.03 g Halsband für Hunde >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Greece	Bayer Animal Health GmbH, 51368 Leverkusen Germany	SERESTO, Περιλαίμιο (1.250 + 0.563)g /περιλαίμιο 38 cm (12.5)g Για γάτες και σκύλους ≤8kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Greece	Bayer Animal Health GmbH, 51368 Leverkusen Germany	SERESTO, Περιλαίμιο (1.250 + 0.563)g/ περιλαίμιο 38 cm (12.5)g Για σκύλους (≤8kg)	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Greece	Bayer Animal Health GmbH, 51368 Leverkusen Germany	SERESTO, Περιλαίμιο (4,500 + 2,025)g/ περιλαίμιο 70 cm (45)g Για σκύλους (>8kg)	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Hungary	Bayer Hungaria Kft., 1123 Budapest, Alkotás u.50, Hungary	Foresto 1,25 g + 0,56 g nyakörv macskáknak és kutyáknak ≤8kg A.U.V.	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Hungary	Bayer Hungaria Kft., 1123 Budapest, Alkotás u.50, Hungary	Foresto 4,50 g + 2,03 g nyakörv kutyáknak >8 kg A.U.V.	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Iceland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 1,25 g/ 0,56 g hálsband fyrir ketti og hunda ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Iceland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 1,25 g/ 0,56 g hálsband fyrir hunda ≤8 kg.	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Iceland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 4,50 g/ 2,03 g hálsband fyrir hunda >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Ireland	Bayer Ltd., The Atrium, Blackthorn Road, Dublin 18, Ireland	Seresto 1,25 g + 0,56 g collar for dogs ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Ireland	Bayer Ltd., The Atrium, Blackthorn Road, Dublin 18, Ireland	Seresto 4,50 g + 2,03 g collar for dogs >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Italy	Bayer S.p.A., Viale Certosa, 130 20156 Milano Italy	Seresto 1,25 g + 0,56 g, collare per cani ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Italy	Bayer S.p.A., Viale Certosa, 130 20156 Milano Italy	Seresto 1,25 g + 0,56 g, collare per cani ≤8 kg e gatti	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Italy	Bayer S.p.A., Viale Certosa, 130 20156 Milano Italy	Seresto 4,50 g + 2,03 g, collare per cani >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Latvia	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 1,25 g + 0,56 g kakla siksna kaķiem un suņiem ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Latvia	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 4,5 g + 2,03 g kakla siksna suņiem >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Lithuania	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 1,25 g + 0,56 g, antkaklis katėms ir šunims iki 8 kg svorio	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 4,50 g + 2,03 g, antkaklis šunims, sveriantiems daugiau kaip 8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Luxembourg	Bayer SA-NV, J.E. Mommaertslaan 14 1831 Diegem (Machelen), Belgium	Seresto 1,25 g+ 0,56 g collier pour chats et chiens ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Luxembourg	Bayer SA-NV, J.E. Mommaertslaan 14 1831 Diegem (Machelen), Belgium	Seresto 1,25 g+ 0,56 g collier pour chiens ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Luxembourg	Bayer SA-NV, J.E. Mommaertslaan 14 1831 Diegem (Machelen), Belgium	Seresto 4,50 g+ 2,03 g collier pour chiens >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Netherlands	Bayer B.V., Animal Health Division Energieweg 1 3641 RT Mijdrecht Netherlands	Seresto 4,50 g + 2,03 g halsband voor honden >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Netherlands	Bayer B.V., Animal Health Division Energieweg 1 3641 RT Mijdrecht Netherlands	Seresto 1,25 g + 0,56 g halsband voor honden ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Netherlands	Bayer B.V., Animal Health Division Energieweg 1 3641 RT Mijdrecht Netherlands	Seresto 1,25 g + 0,56 g halsband voor katten en honden <8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Norway	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 1,25 g / 0,56 g halsbånd til katt og hund ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Norway	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto 1,25 g / 0,56 g halsbånd til hund ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Norway	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. 4,50 g / 2,03 g halsbånd til hund >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Poland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 1,25 g + 0,56 g obroża dla kotów i psów o masie ciala ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Poland	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 4,50 g + 2,03 g obroża dla psow o masie ciala >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Portugal	Bayer Portugal, Lda., Rua Quinta do Pinheiro, 5, 2794-003 Carnaxide Portugal	Seresto coleira 1,25 g + 0,56 g para gatos e cães ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Portugal	Bayer Portugal, Lda., Rua Quinta do Pinheiro, 5, 2794-003 Carnaxide Portugal	Seresto coleira 1,25 g + 0,56 g para cães ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Portugal	Bayer Portugal, Lda., Rua Quinta do Pinheiro, 5, 2794-003 Carnaxide Portugal	Seresto coleira 4,50 g + 2,03 g para cães >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 1.25 g + 0.56 g, zgardă antiparazitară pentru pisici şi câini ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Romania	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Foresto 4.50 g + 2.03 g, g zgardă antiparazitară pentru câini >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Slovakia	Bayer s.r.o., Siemensova 2717/4, 155 80 Praha 5, Czech Republic	Foresto 1,25 g + 0,56 g obojok pre macky a psy ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Slovakia	Bayer s.r.o., Siemensova 2717/4, 155 80 Praha 5, Czech Republic	Foresto 4,50 g + 2,03 g obojok pre psy >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Slovenia	Bayer d.o.o., Bravničarjeva 13 1000 Ljubljana Slovenia	Foresto 1,25 g + 0,56 g, ovratnica za mačke in pse ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Slovenia	Bayer d.o.o., Bravničarjeva 13 1000 Ljubljana Slovenia	Foresto 4,50 g + 2,03 g, ovratnica za pse >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Spain	Bayer Hispania, S.L., Av. Baix Lobregat, 3-5 08970 Sant Joan Despí (Barcelona) Spain	Seresto 1,25 g + 0,56 g collar para perros ≤8 kg y gatos	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Spain	Bayer Hispania, S.L., Av. Baix Lobregat, 3-5 08970 Sant Joan Despí (Barcelona) Spain	Seresto 1,25 g + 0,56 g collar para perros ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Bayer Hispania, S.L., Av. Baix Lobregat, 3-5 08970 Sant Joan Despí (Barcelona) Spain	Seresto 4,50 g + 2,03 g collar para perros >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
Sweden	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet för katt och hund upp till 8 kg, 1,25 g + 0,56 g halsband	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Sweden	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet. för hund upp till 8 kg 1,25 g + 0,56 g halsband	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
Sweden	Bayer Animal Health GmbH, 51368 Leverkusen Germany	Seresto vet för hund över 8 kg 4,50 g + 2,03 g halsband	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use
United Kingdom	Bayer plc, 400 South Oak Way Green Park Reading Berkshire RG2 6AD United Kingdom	Seresto 1,25 + 0,56 collar for cats	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use
United Kingdom	Bayer plc, 400 South Oak Way Green Park Reading Berkshire RG2 6AD United Kingdom	Seresto 1,25 + 0,56 collar for dogs ≤8 kg	imidacloprid/ flumethrin	1.25 g imidacloprid / 0.56 g flumethrin	Collar	Dogs	Cutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Bayer plc, 400 South Oak Way Green Park Reading Berkshire RG2 6AD United Kingdom	Seresto 4,50 + 2,03 collar for dogs >8 kg	imidacloprid/ flumethrin	4.50 g imidacloprid / 2.03 g flumethrin	Collar	Dogs	Cutaneous use

Annex II

Scientific conclusions and grounds for the granting of the variation of the marketing authorisations

Overall summary of the scientific evaluation of Seresto and its associated name Foresto (see Annex I)

1. Introduction

Seresto and its associated name Foresto (thereinafter "Seresto") is a medicated collar containing 10% imidacloprid and 4.5% flumethrin. It is indicated for the treatment and prevention of infestations with fleas, ticks, and lice in dogs and cats, and provides indirect protection against the transmission of the pathogens *Babesia canis vogeli* and *Ehrlichia canis* from the vector tick *Rhipicephalus sanguineus*, thereby reducing the risk of canine babesiosis and canine ehrlichiosis for 7 months.

The marketing authorisation holder (MAH) submitted a variation application to add a new therapeutic indication: "Indirect protection against the transmission of pathogen *Leishmania infantum* by sand flies (*Phlebotomus perniciosus*) thereby reducing the risk of canine leishmaniosis for 7 to 8 months". In support of this application, the MAH provided laboratory and field studies. During the course of the procedure, the indication was amended by the reference Member State (RMS) who stated that 'the demonstration of efficacy of the product against the sand flies over the whole season is a prerequisite for the claimed indirect prevention of transmission of *L. infantum*. Therefore, the new indication of prevention of transmission of *L. infantum* can only be accepted if the vector, i.e. *P. perniciosus* would also be part of the clinical indication'. The indication proposed by the RMS, and agreed by the majority of the concerned Member States (CMSs), at the referral stage was "To significantly reduce the occurrence of infection with *Leishmania infantum* for up to 8 months due to repellent (anti-feeding) action of the product on sand flies."

The United Kingdom considered that, for any vector-borne disease, before an indication can be accepted, demonstration of efficacy against the vector must also be established. In the case of the sand fly and *L. infantum*, the active substances in Seresto, imidacloprid and flumethrin, have no known efficacy against the *Leishmania* parasite and therefore any preventative efficacy against leishmaniosis would be purely as a result of efficacy against the sand fly.

Regarding the data requirement for the demonstration of repellent (anti-feeding) efficacy against *P. perniciosus*, the UK did not accept that the laboratory data submitted by the MAH for the product justify the inclusion of an indication against the sand fly vector. The efficacy threshold of 80–100% (preferably 90%) as recommended in the guideline Demonstration of Efficacy of Ectoparasiticides (7AE17a)[1] was not met at sufficient time points.

The three field studies provided demonstrated that, depending on the infection pressure by sand flies, use of Seresto reduced the risk of infection with *L. infantum* by 88.3–100%. However, as they were conducted in animal shelters in Southern Italy, the UK considered that it is not possible to extrapolate the findings from these studies relating to transmission of leishmaniosis to all areas of the EU where the disease is endemic.

In summary, the UK considered that the efficacy of Seresto for the proposed indication has not been sufficiently demonstrated and that accepting the indication could pose a serious risk to animal and human health.

[1] Guideline Demonstration of Efficacy of Ectoparasiticides (7AE17a) – link

2. Assessment of the data submitted

It should be noted that Guideline 7AE17a provides general guidance including a threshold for efficacy against Diptera, but was not established with the aim of providing guidance on studies to support claims relating to vector-borne diseases such as reduction of canine leishmaniosis. Furthermore, there are specific difficulties inherent in the demonstration of such a claim: there is, at present, no validated laboratory model which can determine the efficacy of a veterinary medicinal product against leishmaniosis.

For the protective claim sought, demonstration of an anti-feeding activity for Seresto against sand flies was considered a prerequisite by the CVMP as the active substances in the Seresto collar, imidacloprid and flumethrin, have no known efficacy against *Leishmania* and therefore, any preventative efficacy against leishmaniosis is purely a result of efficacy against the sand fly. The MAH has provided three GCP-compliant laboratory studies, conducted in order to determine the anti-feeding and insecticidal efficacy of the test product against sand flies. Due to the use of a very low sample size in two of the studies, only one study was considered to have produced reliable results and so the following comments are based on just this study.

In this laboratory study, 14 dogs were randomised to either treatment with Seresto collar (n=7) or untreated control (n=7). The dogs were each infested with 80 female sand flies on 13 occasions (D7, 14, 21, 28, 56, 84, 112, 140, 166, 196, 208, 215, and 222). Repellent efficacy was assessed by comparing the number of fed female sand flies in the treated animals to the number of fed female sand flies in the untreated animals.

According to Guideline 7AE17a, the threshold of efficacy for Diptera should be 80-100% (preferably more than 90%). The anti-feeding results, when using the absolute numbers of sand flies to calculate efficacy using the Abbott's formula as per the recommendation of Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMA/CVMP/EWP/005/2000-Rev.2)[2], averaged 75.1% over the study period (65%-89%). Of the thirteen assessment time points, an anti-feeding efficacy above 80% was only achieved on three occasions. The anti-feeding efficacy demonstrated for Seresto is, therefore, considered insufficient for the inclusion of a direct repellent claim against *P. perniciosus*.

The MAH also provided an alternative analysis of the laboratory data from all 3 studies using ratios of fed to unfed sand flies for efficacy calculation. The use of fed to unfed female sand flies ratios in Abbott's formula is not considered acceptable as a method for calculation of percentage efficacy as ratios have been used incorrectly to approximate risks (probabilities). However, the ratio of fed to unfed sand flies in the laboratory study described above is lower in treated dogs (mean 0.3, range 0.1 to 0.4) when compared to untreated animals (mean 9.0, range 3.3 to 15.6). The consistently low fed to unfed ratios observed in treated dogs, compared to the high and variable fed to unfed ratios in untreated animals, demonstrate that the use of Seresto confers on treated dogs a sustained and consistent anti-feeding effect against sand flies (*P. perniciosus*).

In support of the efficacy of Seresto relating to the transmission or occurrence of *Leishmania infantum* in dogs, the MAH provided three field studies. The first study was a negatively-controlled, randomised, multicentre field study, which was partially blinded. A total of 279 dogs, of several breeds and aged between 2 and 96 months, were enrolled on day 0, with 219 of these dogs included in the efficacy calculation. The study duration was 300 days ± 10 days, and the treated animals wore the collar for the first 210 ± 10 days of this period. Animals were tested for leishmaniosis with samples of blood and

[2] Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMA/CVMP/EWP/005/2000-Rev.2) – link

skin tissue being collected on study days 0, 90, 180, 210, and 300 (i.e. in the post-treatment phase), and samples of bone marrow collected on study days 0 and D300. Positive animals were defined as the animals that at study completion were positive to one or more of the following tests: serology for circulating anti-*Leishmania-infantum*-antibodies (IFAT), cytology/PCR on skin tissue sample, and cytology/PCR of bone marrow aspirate. Efficacy evaluation was based on the comparison of the percentage of animals infected by *L. infantum* in the treated and untreated groups at the end of the study.

The second field study was a negatively-controlled, single centre, partially-blinded, clinical field study. A total of 122 dogs, of several breeds aged between 1.5 and 6 months, were enrolled (mostly as litters) on individual start dates between March and May 2011. The study ran between March 2011 and April 2012, with a post-treatment phase commencing April 2012 and completing October 2012. Treated dogs were continually treated with Seresto throughout the study period, with the collar being replaced as necessary due to growth of the animal or according to the label instructions for the product. Animals were tested for leishmaniosis with samples of blood and skin tissue being collected on study day 0, in July 2011, September 2011, November 2011, April 2012, and October 2012. Conjunctival swabs were collected on study day 0 and samples of bone marrow were collected on study day 0, in April 2012, and October 2012. An animal was considered positive for leishmaniosis if positive to one or more tests used. Efficacy evaluation was based on the comparison of the percentage of animals infected by *L. infantum* in the treated and untreated groups at the end of the study.

The third field study was a double positive and negative controlled, partially blinded, randomised multicentre field study. A total of 224 dogs, of several breeds and aged between 7 and 77 weeks, were enrolled, blocked by pens and pens were randomised to one of four groups. The study ran between April/May and December 2013 (approximately eight months), and there was a post-treatment phase which ran until April/May 2014. Animals were tested for leishmaniosis with samples of blood and skin tissue being collected on study days 0, 120, 210, and 360 (i.e. in the post-treatment phase), and samples of bone marrow collected on study days 0, 210, and 300. Animals were defined as non-infected by *Leishmania* when seronegative for circulating anti-*L. infantum* antibodies and negative to PCR of skin tissue and bone marrow aspirate samples. Efficacy evaluation for Seresto was based on the comparison of the percentage of animals infected by *L. infantum* in the Seresto treated and untreated groups at the end of the study.

Regarding the results of the three field studies presented by the MAH, all three studies were able to demonstrate that use of Seresto led to a significant reduction in the occurrence of infection with *L. infantum* over a sustained period (between 7 and 8 months), with overall mean efficacies of the collar in preventing leishmaniosis of 93.4% in the first field study, 100% in the second field study, and 88.3% in the third field study as evaluated by the incidence density rate. In the same studies, the incidence density rates in untreated dogs (60.7%, 46.2% and 67.0% respectively) demonstrated the high infection pressure present in the field situations used.

All three field studies were performed in animal shelter situations within a limited geographical area. Both Guideline 7AE17a and Guideline EMEA/CVMP/EWP/005/2000-Rev.2 state that field studies should be performed in at least two geographical regions and the animal population studied should be representative of the target population. However, it was agreed by the CVMP that the field situations used in the studies submitted represent a ‘worst case scenario’ in terms of exposure to infected sand flies: there was a high level of exposure to infected sand flies (incidence density rates in untreated dogs varied between 46.2 to 67.0%); dogs were housed outside throughout the day and night leading to unrestricted contact between the host and the vector; untreated dogs housed at the study area but not enrolled in the study constituted an additional reservoir for leishmaniosis. Most dogs in normal household situations in countries endemic for leishmaniosis would be expected to be exposed to sand

flies infected with leishmaniosis to a substantially lower extent, and therefore it was considered possible to extrapolate the results with confidence to the general target population.

Having considered all of the data and argumentation submitted, it was the opinion of the CVMP that, although the MAH has not demonstrated that Seresto has satisfactory anti-feeding efficacy against *P. perniciosus* that would support a direct repellent claim against this parasite, the studies provided demonstrate that dogs treated with Seresto have a significant reduction in the occurrence of infection with *L. infantum* as a result of reduced transmission by the sand fly vector. Therefore, whilst it was concluded that the claim 'to significantly reduce the occurrence of infection with *Leishmania infantum* for up to 8 months due to repellent (anti-feeding) action of the product on sand flies' should not be included in the SPC, an amended indication, which accurately reflects the data provided, 'reduction of the risk of infection with *Leishmania infantum* via transmission by sand flies for up to 8 months' was considered acceptable.

3. Benefit-risk assessment

Introduction

Seresto contains the active substances imidacloprid 10% and flumethrin 4.5%.

The application was submitted as a Type II variation for the addition of the new therapeutic indication 'to significantly reduce the occurrence of infection with *Leishmania infantum* for up to 8 months due to repellent (anti-feeding) action of the product on sand flies'. The benefit-risk assessment is made on this basis.

Benefit assessment

Three field studies, performed in situations with high infection pressure for leishmaniosis, demonstrated that the occurrence of new cases of *L. infantum* is significantly reduced in dogs treated with Seresto. Laboratory studies did not demonstrate a sufficient anti-feeding (repellent) effect against sand flies (*P. perniciosus*) to support a direct indication against the sand fly. However, the consistently low ratios of fed to unfed females seen in the laboratory studies are considered supportive of the field studies results. A claim for 'reduction of the risk of infection with *Leishmania infantum* via transmission by sand flies for up to 8 months' has been adequately demonstrated. Although a significant reduction in the incidence of *L. infantum* in dogs has been demonstrated, the product has shown variable repellent (anti-feeding) and insecticidal efficacy against the sand fly *P. perniciosus*. As a result, bites by sand flies may occur, and the transmission of *L. infantum* cannot be completely excluded.

Relevant information relating to the supporting studies should be added to the SPC.

Risk assessment

This is a variation application for an already-authorised product (Seresto); no further risks have been identified in the studies provided. All risks relating to the target animal, the user and the environment are adequately addressed in the product literature.

Evaluation of the benefit-risk balance

The benefit-risk balance for the agreed indication is considered favourable.

Conclusion on the benefit-risk balance

Based on the data presented, the CVMP concluded that the efficacy of Seresto, and its associated name Foresto, with regard to a reduction of infection with *L. infantum* has been demonstrated, and that the benefit-risk balance is favourable.

Grounds for the granting of the variation of the marketing authorisations

Whereas

- the CVMP considered that the efficacy of Seresto, and its associated name Foresto, relating to repellent (anti-feeding) activity against sand flies (*Phlebotomus perniciosus*) has not been satisfactorily demonstrated in the laboratory studies provided;
- the CVMP considered that the efficacy of Seresto, and its associated name Foresto, relating to the transmission or occurrence of *Leishmania infantum* in dogs has been satisfactorily demonstrated in the field studies provided;
- the CVMP considered that the consistently low ratios of fed to unfed female sand flies seen in the laboratory studies are regarded supportive of the field study results;

the CVMP has recommended the granting of the variation of the marketing authorisations for Seresto and its associated name Foresto with amendment to the summary of product characteristics, labelling and package leaflet of the reference Member State. The amended summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Amendments in the relevant sections of the summary of product characteristics and package leaflet

The valid summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination Group procedure with the following amendments:

Add the following text in the relevant sections of the product information:

Summary of product characteristics

4.2 Indications for use, specifying the target species

Reduction of the risk of infection with *Leishmania infantum* via transmission by sand flies for up to 8 months.

4.4 Special warnings for each target species

Although a significant reduction in the incidence of *Leishmania infantum* in dogs has been demonstrated, the product has shown variable repellent (anti-feeding) and insecticidal efficacy against the sand fly *Phlebotomus perniciosus*. As a result, bites by sand flies may occur, and the transmission of *Leishmania infantum* cannot be completely excluded. The collar should be applied just before the beginning of the period of activity of sand fly vectors corresponding to the *Leishmania infantum* transmission season and worn continuously throughout the risk period.

The influence of shampooing or water immersion regarding the transmission of canine leishmaniosis has not been examined.

5.1 Pharmacodynamic properties

Data from efficacy studies against sand flies (*Phlebotomus perniciosus*) showed a variable sand fly repellent (anti-feeding) efficacy ranging from 65 to 89% for 7-8 months following initial application of the collar. Data from 3 clinical field studies performed in endemic areas indicate a significant reduction in the risk of *Leishmania infantum* transmission by sand flies in treated dogs compared to non-treated dogs. Depending on the infection pressure by sand flies the efficacy in the reduction of the risk of infection with leishmaniosis ranged from 88.3 to 100%.

Package leaflet

4 INDICATIONS

Reduction of the risk of infection with *Leishmania infantum* via transmission by sand flies for up to 8 months.

12 SPECIAL WARNING(S)

Special warnings for each target species

Although a significant reduction in the incidence of *Leishmania infantum* in dogs has been demonstrated, the product has shown variable repellent (anti-feeding) and insecticidal efficacy against the sand fly *Phlebotomus perniciosus*. As a result, bites by sand flies may occur, and the transmission of *Leishmania infantum* cannot be completely excluded. The collar should be applied just before the beginning of the period of activity of sand fly vectors corresponding to the *Leishmania infantum* transmission season and worn continuously throughout the risk period.

The influence of shampooing or water immersion regarding the transmission of canine leishmaniosis has not been examined.

15 OTHER INFORMATION

Data from efficacy studies against sand flies (*Phlebotomus perniciosus*) showed a variable sand fly repellent (anti-feeding) efficacy ranging from 65 to 89% for 7-8 months following initial application of the collar. Data from 3 clinical field studies performed in endemic areas indicate a significant reduction in the risk of *Leishmania infantum* transmission by sand flies in treated dogs compared to non-treated dogs. Depending on the infection pressure by sand flies the efficacy in the reduction of the risk of infection with leishmaniosis ranged from 88.3 to 100%.