ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Wellplus Flavoured Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0352/001/DC
Name, strength and pharmaceutical form	Wellplus Flavoured Tablets for Dogs
Applicant	Divasa – Farmavic SA Ctra. Sant Hipolit KM71 PO Box 79 08503 Gurb-Vic Barcelona Spain
Active substance(s)	Praziquantel Pyrantel embonate Febantel
ATC Vetcode	QP52AC55
Target species	Dogs
Indication for use	For the treatment of mixed infestations with the following roundworms and tapeworms in dogs and puppies: Ascarids: *Toxocara canis, Toxacaris leonina* (adult and late immature forms) Hookworms: *Uncinaria stenocephala, Ancylostoma caninum* (adults) Tapeworms: *Echinococcus granulosus, Echinococcus multilocularis, Dipylidium caninum, Taenia* spp., *Multiceps multiceps* (adult and immature forms)

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23rd October 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Belgium, Bulgaria, Germany, Greece, Ireland, the Netherlands, Poland, Portugal, Romania, Slovakia, Spain

I. SCIENTIFIC OVERVIEW

Wellplus Flavoured Tablets for Dogs have been developed as a generic hybrid of Drontal Plus Flavour Bone Shaped Tablets. The product contains three active substances; 150 mg febantel, 50 mg praziquantel and 144 mg pyrantel embonate. Wellplus Flavoured Tablets are indicated for the treatment of gastrointestinal tapeworms and roundworms in dogs and puppies. The product is contraindicated for simultaneous use with piperazine compounds and in cases of known hypersensitivity to any of the active substances or excipients.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species.

The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substances praziquantel, pyrantel embonate and febantel. The excipients are maize starch, lactose monohydrate, microcrystalline cellulose, povidone K29/32, magnesium stearate, sodium laurilsulfate, meat flavour and silica, colloidal anhydrous.

The container/closure system consists of PVC/PVDC aluminium blister containing 2 or 10 tablets packaged in a cardboard carton of either 2, 10, 20, 50, 100 and 300 tablets. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing the ingredients before granulating and drying the granules. The remaining ingredients are then added to the dried granules and blended before the tablets are compressed. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances, febantel, praziquantel and pyrantel embonate, are established active substances described in the European Pharmacopoeia. Certificates of Suitability have been provided for each of the manufacturers of the active substances. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients comply with their respective Ph. Eur. monographs, except for the meat flavour which is not described in a Ph. Eur. monograph. An in-house specification has been provided instead. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of

Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include those for appearance, colour, odour and dimensions as well as identification and assay of the active substance, identification of impurities, hardness, dissolution and microbial count.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 5 years is specified for febantel and pyrantel embonate, whilst the retest interval for praziquantel is 36 months.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Three batches were stored at 25°C/60%RH for 48 months and under accelerated condition for 6 months (40°C/75%RH). The product was found to be stable and a shelf life of 5 years has been established. The in-use stability was also investigated and shelf life of 15 days is supported for the broached package and part used tablets.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale: 5 years.
- Shelf life after first opening the immediate packaging: 15 days.
- Shelf life after dividing the tablet into halves or quarters: 15 days.
- Return any part tablet to the open blister pack.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics
As this is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been confirmed, pharmacodynamic data were not required. The pharmacodynamics profiles of the three active substances febantel, praziquantel and pyrantel embonate are extensively published in the literature and no further information is necessary.

Pharmacokinetics
The product has the same composition as the reference product and the same pharmaceutical form. Bioequivalence has been confirmed for praziquantel. Bioequivalence criteria could not be fulfilled through bioavailability studies due to poor absorption of febantel and pyrantel embonate from the gastrointestinal tract. Instead dose confirmation studies were performed to demonstrate bioequivalence. These studies are covered in the Efficacy section of this report.

Toxicological Studies

As this is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence has been confirmed, results of toxicological studies were not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is essentially similar to the reference product with the same user risks. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- In case of accidental ingestion, seek medical advice immediately and show package leaflet or the label to the physician.
- Wash hands after use.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is intended for oral administration to non-food animals (dogs) only therefore it is not expected to pose a risk to the environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The product contains a fixed-dose combination of three active substances; febantel, pyrantel embonate and praziquantel. Febantel does not act as an anthelmintic directly but disrupts the parasite's metabolism by inhibiting tubular polymerisation which leads to the death of the parasite. Pyrantel embonate causes spastic paralysis through a depolarising neuromuscular blockade. Praziquantel severely damages the parasite integument which results in contraction and paralysis of the parasite. Febantel and pyrantel embonate demonstate synergistic activity against hookworms and ascarids tested in puppies and young dogs.

Pharmacokinetics
An *in vivo* bioequivalence study was performed to compare the test product against the reference product. The study aimed to compare the bioavailability of the active substances (febantel, pyrantel embonate and praziquantel) in dogs. The study saw either the test or reference product orally administered to 12 Beagle dogs following an 18 hour fast. Seven days later the study was repeated with the dogs given the other product compared to the first round, i.e. Group 1 received the test product on day 0 and the reference product on day 7 and vice versa. Blood samples were taken before the treatment and at regular intervals following administration of the product up to 48 hours post-treatment.

The C_{max}[1], AUC[2] and $t_{1/2}$[3] were measured and the 90% confidence interval was calculated for C_{max} and AUC. The study demonstrated bioequivalence in the measured parameters for praziquantel but the 90% confidence interval fell outside the acceptable range for febantel and pyrantel embonate. This is thought to be due to poor GI absorption of these two substances resulting in variability of plasma level and plasma levels are not directly related to therapeutic effect as the site of activity for all therapeutic claims is in the gut. Therefore dose confirmation studies were presented to demonstrate efficacy of the test product against ascarids and hookworms.

Tolerance in the Target Species of Animals

This is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product. The three active substances are widely used in veterinary medicine and published literature supports the safety.

[1] C_{max} – Maximum plasma concentration
[2] AUC – Area under the curve
[3] $t_{1/2}$ – Half life

Resistance

The references provided show that there is no known resistance to febantel in the target parasites. Similarly with praziquantel there is no known resistance in dogs, however there are reports of resistance in humans. It was also identified that resistance has been described in hookworms to pyrantel. The reports suggest resistance occurs through modification of the pyrantel receptor properties of the parasite. However no reports of resistance to any of the active substances by the target species in Europe have been identified. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted four dose confirmation studies to demonstrate the efficacy of febantel and pyrantel embonate. Bioequivalence has been claimed for praziquantel.

Dose confirmation studies:

Study title	Dose confirmation study on the efficacy of a praziquantel/febantel/pyrantel combination tablet against L3/L4 stages of *Toxacara canis* in experimentally infected dogs
Objectives	To confirm the anthelmintic efficacy of an orally administered praziquantel/febantel/pyrantel combination tablet against L3/L4 developmental stages of *Toxacara canis*.
Test site(s)	Single centre, CRO, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	The test product, Wellplus Flavour Tablets for Dogs was administered orally at a dose of ¼ of a tablet per 2.5 kg of bodyweight.
Control product/placebo	A negative control was used where a group of dogs received no treatment.
Animals	24 healthy cross-bred domestic dogs, aged 7-10 weeks were used in the study. Dogs were free of resident nematodes at the start of the study.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the test product. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised.
Blinding	Personnel involved in collecting the data were blinded.
Method	Dogs were acclimatised for 7 days and faecal flotation was used to determine they were free of nematodes. Dogs were then infected with 300-500 *T. canis* larvated

	eggs. All 24 dogs were infected then divided into three groups of 8. Group 1 acted as control and received no treatment. Group 2 received treatment on Day 5 and Group 3 were treated on Day 21. Necropsy was performed on Day 28. Clinical observations were made during the acclimatisation period, following infection and after treatment was administered. At necropsy gastrointestinal helminths were removed for identification and enumeration.
Statistical method	Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from treatment groups compared to the negative control group. The efficacy was calculated separately for L3 and L4 larvae. Natural logarithm transformed counts, plus 1, were analysed using a general linear model. Treatment was modelled as a fixed effect with block as a random effect. Least squares means of the log-transformed counts were then compared between the treatment and control groups. The data was back transformed to calculate the geometric mean and percent effectiveness. A p value of <0.05 was used to determine statistical significance.
RESULTS	
Outcomes for endpoints	The mean number of worms present in dogs in Groups 1, 2 and 3 were calculated. The geometric mean for Group 1 (control) was 5.2, for Group 2 = 10.1 and for Group 3 = 0. The percent efficacy was calculated as 0% for Group 2 and 100% for Group 3. A statistically significant difference was identified between Group 1 and 3 ($p=0.0002$) and between Group 2 and 3 ($p<0.0001$). There was no statistical difference between Group 1 and 2 ($p>0.1$).
DISCUSSION	The treatment was considered effective if there was statistically significant differences between treated and control groups, following adequate infection of the dogs, and if the percent effectiveness was >90%. The level of infection was determined to be adequate based on control group data. The results showed the treatment was ineffective against early larval stages when administered at 5 days after experimental infection. However when administered 21 days after infection the test product is 100% effective against late immature larval stages and immature adult stages of *T. canis*. No adverse events were observed as a result of treatment.

Study title	Dose confirmation study on the efficacy of a praziquantel/febantel/pyrantel combination tablet against *Toxacara canis* in naturally infected dogs
Objectives	To confirm the anthelmintic efficacy of an orally administered praziquantel/febantel/pyrantel combination tablet against *Toxacara canis* in naturally infected dogs.
Test site(s)	Single centre, CRO, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	The test product, Wellplus Flavour Tablets for Dogs was administered orally at a dose of ¼ of a tablet per 2.5 kg of bodyweight.
Control product/placebo	A negative control was used.
Animals	20 cross-bred domestic dogs, aged below 16 weeks were used in the study. Dogs were selected if *T.canis* infection was demonstrated through faecal egg counts and provided they had not been treated with an anthelmintic within 10 days prior to the acclimatisation period of the study.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the test product. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised.
Blinding	Personnel involved in collecting the data were blinded.
Method	Dogs were acclimatised for 7 days and faecal egg counts were used to determine the mean pre-treatment egg count. Dogs were divided into two groups of 10 animals. Group 1 acted as the negative control and received no treatment, whilst Group 2 received the test product. Faecal egg counts and necropsy were performed on Day 7. Clinical observations were made during the acclimatisation period, following infection and after treatment was administered. At necropsy gastrointestinal helminths were removed for identification and enumeration.
Statistical method	Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from treatment groups compared to the negative control group. Natural logarithm transformed counts, plus 1, were analysed using a general linear model. Treatment was modelled as a fixed effect with block as a random effect. Least squares means of the log-transformed counts were then compared between the treatment and control groups. The data was back transformed to calculate the geometric mean and percent effectiveness. A p value of

	<0.05 was used to determine statistical significance. In addition percentage reduction of faecal egg counts was calculated in the treated animals using pre- and post-treatment egg counts. Again a p value of <0.05 was used.
RESULTS	
Outcomes for endpoints	Faecal egg counts were compared between the treatment and control groups. The mean percentage reduction in the treated animals by Day 7 was 100%. The mean number of worms present in dogs at the end of the study in both groups was calculated. The geometric mean for Group 1 (control) was 16.5 and for Group 2 was 0.4. The percentage effectiveness was calculated as 97.3%. A statistically significant difference was identified between the worm counts for Group 1 and 2 (p=0.0001).
DISCUSSION	The treatment was considered effective if there was statistically significant differences between treated and control groups, following adequate infection of the dogs, and if the percent effectiveness was >90%. The level of infection was determined to be adequate based on control group data. The results demonstrate the test product is effective against *T. canis*. The dogs tolerated the treatment well and no adverse events were observed as a result of treatment.

Study title	Dose confirmation study on the efficacy of a praziquantel/febantel/pyrantel combination tablet against *Ancylostoma caninum* in naturally infected dogs
Objectives	To confirm the anthelmintic efficacy of an orally administered praziquantel/febantel/pyrantel combination tablet against *Ancylostoma caninum* in naturally infected dogs.
Test site(s)	Single centre, CRO, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	The test product, Wellplus Flavour Tablets for Dogs was administered orally at a dose of ¼ of a tablet per 2.5 kg of bodyweight.
Control product/placebo	A negative control was used.
Animals	16 cross-bred domestic dogs, aged over 6 weeks were used in the study. Dogs were selected if *A. caninum* infection was demonstrated through faecal egg counts and provided they had not been treated with an anthelmintic within 10 days prior to the acclimatisation period of the study. It

	was also checked that female dogs were not pregnant.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the test product. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised.
Blinding	Personnel involved in collecting the data were blinded.
Method	Dogs were acclimatised for 7 days and faecal egg counts were used to determine the mean pre-treatment egg count. Dogs were divided into two groups of 8 animals. Group 1 acted as the negative control and received no treatment, whilst Group 2 received the test product. Faecal egg counts and necropsy were performed on Day 7. Clinical observations were made during the acclimatisation period, following infection and after treatment was administered. At necropsy gastrointestinal helminths were removed for identification and enumeration.
Statistical method	Efficacy calculations were used to determine the effectiveness of treatment. These were based on the number of worms recovered from treatment groups compared to the negative control group. Natural logarithm transformed counts, plus 1, were analysed using a general linear model. Treatment was modelled as a fixed effect with block as a random effect. Least squares means of the log-transformed counts were then compared between the treatment and control groups. The data was back transformed to calculate the geometric mean and percent effectiveness. A p value of <0.05 was used to determine statistical significance. In addition percentage reduction of faecal egg counts was calculated in the treated animals using pre- and post-treatment egg counts. Again a p value of <0.05 was used.
RESULTS	
Outcomes for endpoints	Faecal egg counts were compared between the treatment and control groups. The mean percentage reduction in the treated animals by Day 7 was 100%. The mean number of worms present in dogs at the end of the study in both groups was calculated. The geometric mean for Group 1 (control) was 37.8 and for Group 2 was 0.1. The percentage effectiveness was calculated as 99.8%. A statistically significant difference was identified between the worm counts for Group 1 and 2 (p=0.0001).
DISCUSSION	The treatment was considered effective if there was statistically significant differences between treated and control groups, following adequate infection of the dogs, and if the percent effectiveness was >90%. The level of

	infection was determined to be adequate based on control group data. The results demonstrate the test product is effective against *A. caninum*. The dogs tolerated the treatment well and no adverse events were observed as a result of treatment.

Study title	Dose confirmation study on the efficacy of a praziquantel/febantel/pyrantel combination tablet against *Trichuris vulpis* and hookworms in naturally infected dogs
Objectives	To confirm the anthelmintic efficacy of an orally administered praziquantel/febantel/pyrantel combination tablet against *Trichuris vulpis* and hookworms in naturally infected dogs.
Test site(s)	Single centre, CRO, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	The test product, Wellplus Flavour Tablets for Dogs was administered orally at a dose of ¼ of a tablet per 2.5 kg of bodyweight.
Control product/placebo	A negative control was used.
Animals	16 cross-bred domestic dogs were used in the study. Dogs were selected if *T. vulpis* and hookworm infection was demonstrated through faecal egg counts and provided they had not been treated with an anthelmintic within 10 days prior to the acclimatisation period of the study. It was also checked that female dogs were not pregnant.
Outcomes/endpoints	The primary endpoint was the percentage effectiveness of the test product. This was calculated as the percentage of worms in treated animals compared to control animals.
Randomisation	Randomised.
Blinding	Personnel involved in collecting the data were blinded.
Method	Dogs were acclimatised for 7 days and faecal egg counts were used to determine the mean pre-treatment egg count. Dogs were divided into two groups of 8 animals. Group 1 acted as the negative control and received no treatment, whilst Group 2 received the test product. Faecal egg counts and necropsy were performed on Day 7. Clinical observations were made during the acclimatisation period, following infection and after treatment was administered. At necropsy gastrointestinal helminths were removed for identification and enumeration.
Statistical method	Efficacy calculations were used to determine the effectiveness of treatment. These were based on the

	number of worms recovered from treatment groups compared to the negative control group. Natural logarithm transformed counts, plus 1, were analysed using a general linear model. Treatment was modelled as a fixed effect with block as a random effect. Least squares means of the log-transformed counts were then compared between the treatment and control groups. The data was back transformed to calculate the geometric mean and percent effectiveness. A p value of <0.05 was used to determine statistical significance. In addition percentage reduction of faecal egg counts was calculated in the treated animals using pre- and post-treatment egg counts. Again a p value of <0.05 was used.
RESULTS	
Outcomes for endpoints	Faecal egg counts and worm counts were compared between the treatment and control groups. The mean number of *T. vulpis* worms present in dogs at the end of the study in both groups was calculated. The percentage effectiveness was calculated as 48.4% against *T. vulpis* and the difference between worm counts in Groups 1 and 2 was not statistically significant (p>0.1). *Uncinaria stenocephala* infection was also identified in the dogs. The pre- and post-treatment egg counts were compared in the test group. The mean percentage reduction in treated animals by Day 7 was 86.20% but compared to negative control the percentage reduction was 95.88%. The mean number of *U. stenocephala* worms were counted at necropsy and compared between the control and test groups. The geometric mean for Group 1 was 181.3 and for Group 2 was 5.5. The percentage effectiveness was calculated as 97.0% against *U. stenocephala.* A statistically significant difference was identified between the worm counts for Group 1 and 2 (p=0.0004).
DISCUSSION	The treatment was considered effective if there was statistically significant differences between treated and control groups, following adequate infection of the dogs, and if the percent effectiveness was >90%. The level of infection was determined to be adequate based on control group data. The results demonstrate the test product was not effective against *T. vulpis* but was effective against *U. stenocephala.* No efficacy claims against *T. vulpis* have been made in the SPC. The dogs

	tolerated the treatment well and no adverse events were observed as a result of treatment.

The studies conducted supported the claims in the authorised SPC, in compliance with the requirements laid out in the Guideline for the testing and evaluation of the efficacy of anti-parasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats EMEA/CVMP/EWP/005/2000-Rev.2 June 2008.

Field Trials

As this is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of field studies were not required.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

None