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College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

HuveGuard MMAT

Created: March 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0206/001/MR
Name, strength and pharmaceutical form	HuveGuard MMAT suspension for oral suspension
Applicant	Huvepharma NV Uitbreidingstraat 80 2650 Antwerp Belgium
Active substance(s)	Oocysts of precocious strains of coccidia species: - *Eimeria acervulina* - *Eimeria maxima* - *Eimeria mitis* - *Eimeria tenella*
ATC Vetcode	QI01AN01
Target species	Chicken
Indication for use	For the active immunisation of chickens to reduce infection and clinical signs of coccidiosis caused by *E.acervulina, E.maxima, E. mitis* and *E.tenella.*

HuveGuard MMAT	NL/V/0206/001/MR
Huvepharma NV	MRP
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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	25 May 2016
Date product first authorised in the Reference Member State (MRP only)	27 August 2015
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK

I. SCIENTIFIC OVERVIEW

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, the consumer of foodstuffs from treated animals 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains a minimum of 50 sporulated oocysts of *Eimeria acervulina* strain RA_{3+20}, 100 sporulated oocysts of *Eimeria maxima* strain MCK_{+10}, 100 sporulated oocysts of *Eimeria mitis* strain $Jormit_{3+9}$, and 150 sporulated oocysts of *Eimeria tenella* strain Rt_{3+15} and the excipients sodium chloride, potassium chloride, disodium hydrogen orthophosphate, potassium dihydrogen phosphate, Polysorbate 80 and Water for Injections.
The container/closure system consists of 30 ml low-density polyethylene (LDPE) vials that are closed with rubber stoppers and sealed with aluminium caps. Bottles, stoppers and caps are sterilized by gamma irradiation. The container of 30 ml is used either to hold 1,000 or 5,000 doses in a volume of 25.2 ± 0.2 ml.
The choice of the vaccine strains and excipients are justified.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

HuveGuard MMAT	NL/V/0206/001/MR
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The active substances are oocysts of the coccidia species: *Eimeria acervulina, Eimeria maxima, Eimeria mitis and Eimeria tenella.* The active substance is manufactured in accordance with the principles of good manufacturing practice.
Starting materials of non-biological origin used in production comply with Ph. Eur. monographs where these exist. For the substances where there is no such requirement the company has identified the source of the substance, explained how its quality is controlled and provided relevant certificates of analysis.
Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. Guidelines; any deviation was adequately justified.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular: Appearance, *In vitro* Potency test (viable oocyst count), Sterility, Rapid Potency Test (*in vivo* potency including identity).
The demonstration of the batch to batch consistency is based on the results of 6 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions. 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.

The in-use shelf-life of the vaccine is supported by the data provided.

G. Other Information

None.

III. SAFETY ASSESSMENT

Laboratory trials

Three laboratory safety studies were performed, in accordance with GLP and Ph. Eur. 2326. The safety of the administration of an overdose in the target animal is demonstrated. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. Three studies are performed in which a ten-fold overdose of the vaccine is administered by oral gavage or eye drop to day old, 14 day old and 15 day old SPF chickens. All three studies showed that birds receiving a tenfold overdose of the vaccine did not show clinical signs of coccidiosis in a 21 day period post vaccination. Tests for residual pathogenicity were performed for *E. acervulina, E. maxima, E. mitis* and *E. tenella.* All species complied with the Ph. Eur. 2326 test for residual pathogenicity. Safety of the administration of one dose has not been tested, as the safety of a tenfold overdose was shown. The safety of repeated administration of one dose has not been tested, as the vaccination schedule is for one single dose (no booster dose required) for the life of a broiler, breeder or layer chicken as coccidiosis vaccines rely on natural cycling of the vaccine antigens via the litter for continued stimulation of the immune system.

No investigation of effect on reproductive performance was conducted because the active substances contained in the product are not considered a potential risk factor. No studies have been performed in birds during lay, a relevant warning is included in the SPC.

To examine whether the product might affect the immune system of the vaccinated animal, serological titres after vaccination against Infectious Bronchitis and Newcastle Disease were determined following vaccination with HuveGuard MMAT compared with serological titres following vaccination with Paracox and Hipracox broilers. The data provided, in combination with the known biological properties of *Eimeria spp.*, provide sufficient evidence to support the conclusion that the vaccine is highly unlikely to negatively affect immunological functions.

Spread and dissemination of each vaccine strain included in the vaccine was addressed using bibliographic data. The vaccine strains will spread to unvaccinated birds. Spread to non-target species or dissemination to sites beyond the gut is not known to occur for any Eimeria species of chickens. Appropriate warnings regarding spread as well as measures to limit inadvertent spread of the vaccine strain are included in the SPC. No evidence of reversion to virulence was found in studies carried out for each attenuated vaccine strain.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field studies

Field studies were performed in order to confirm efficacy of HuveGuard MMAT under field conditions and to evaluate safety. Eleven studies were performed in total, in which 13 flocks in total were vaccinated with HuveGuard MMAT in Belgium, The Netherlands and Germany. To monitor safety, animals were observed for Adverse Events on a daily basis.Mortality rates were also considered a measurement of safety. On each trial site at least one house was vaccinated with HuveGuard MMAT and at least one house was vaccinated with Paracox-5 or Hipracox Broilers.
No adverse events were reported in any of the HuveGuard MMAT flocks nor in any of the positive control flocks. A relationship between mortality in the respective treatment groups and the administration of the vaccines could not be established. Also no relationship between the administration of the respective vaccines and occurring diseases or clinical signs of coccidioses could be established. It may be concluded that the safety of the product when administered via spray on feed, spray on chicks, drinking water or eye drop to one day old chicks is comparable with the safety of the positive controls.

User Safety

HuveGuard MMAT	NL/V/0206/001/MR
Huvepharma NV	MRP
	Publicly available assessment report

A user safety risk assessment was conducted in accordance with the appropriate Guideline. The overall risk associated with exposure of users to the product is considered negligible. Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Residue Studies

The excipients used are considered as not falling within the scope of the MRL regulation. Based on this information, no withdrawal period is proposed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated using 12 laboratory studies in accordance with the relevant requirements.

Vaccine batches, at the furthest passage level to be used in production were used in efficacy studies. These vaccine batches were diluted to contain the minimum titre per dose.

The efficacy was evaluated in challenge experiments; separate studies were conducted for each *Eimeria* species contained in the vaccine.

Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:**	
Study					**Vaccinates**	**Controls**
Immunogenicity of E. acervulina RA (EPL 2010-08)						
Chickens One day old Negative control (unvaccinated, unchallenged): 20 Positive control (unvaccinated, unchallenged): 20 Vaccinates, spray on bird: 18	SPF	Spray on chickens on D0 50 oocysts/dose *E. Acervulina* RA as X+8 passage level	21 days PV Strain *E. acervulina* Medace 10^5 oocysts per bird, by oral gavage	28 days: euthanasia for 10 birds in all three groups 35 days: euthanasia remaining birds - Faecal excretion of oocysts - Weight gain - Intestinal lesions	Oocyst output decreased when compared to positive control[a] (Ph. Eur. compliant) Not different from pos control [b] (Not Ph. Eur. compliant) No lesions detected (Ph. Eur. compliant)	Neg control no (100%); Pos control: yes (100%) Pos control less than neg control [a] Neg control: no lesions Pos control: 7 days PC, 90% had lesion score of 3 and 10% of 2 (Ph. Eur. compliant).
Immunogenicity of E. acervulina RA (EPL 2010-06)						

Chickens One day old Negative control (unvaccinated, unchallenged): 20 Positive control (unvaccinated, challenged): 20 Vaccinated1, drinking water: 20 Vaccinated2,	SPF	Spray on feed and spray on chicken, drinking water on D3 Final product used for vaccination Test antigen: *E. acervulina* RA at passage level X+8, 50 oocysts per dose,	Day 21 of study (drinking water 18 days PV; spray 21 days PV) Strain *E. acervulina* Medace 100,000 oocysts per dose by oral gavage	Day 28: 10 birds euthanized Day 35: 10 birds euthanized. - Faecal excretion of oocysts - Weight gain - Intestinal lesions	Decreased for all three vaccinated groups when compared to positive control[a]. (Ph. Eur compliant) No difference to positive control[b]; except for the drinking water group at day 21-28 only[a]. (Not Ph. Eur. compliant) 100% of birds from all vaccinated	Neg control: no Pos control: yes Positive control less than negative control [a] Positive control: on day 7 PC 90%
spray on feed: 20 Vaccinated3, spray on bird: 20					groups had a lesion score of 0. On day 28 and day 35 (Ph. Eur. compliant)	had a lesion score of 3 and 10% of 2. On day 14 PC all birds had a lesion score of 0. (Ph. Eur. compliant)
Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:** Vaccinates	**Results:** Controls
Immunogenicity of E. acervulina RA (EPL 2011-13)						

Chickens One day old Positive control (unvaccinated): 23 Vaccinated1, eye drop: 23 Vaccinated2, drinking water: 23 Vaccinated3, spray on feed: 23 Vaccinated4, spray on bird: 23	SPF	Eye drop, spray on feed on D0, spray on chickens on D0, drinking water on D3 Final product used for vaccination. Test antigen: *E. acervulina* as X+8 passage level, 50 oocyts/dose	Day 21 of study (drinking water 18 days PV; spray and eye drop 21 days PV Strain *E. acervulina* Ponace	7 days post challenge (PC): euthanasia for 10 birds in all three groups 14 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts - Weight gain - Intestinal lesions	Decreased when compared to positive control[a] (Ph. Eur. compliant) spray on chick group higher weight gain compared to the positive control at day 7 PC[a] and the eyedrop group higher weight gain compared to the positive controls at 14 days PC[a] 2 birds with low lesion score at 7 days PC in eye drop group (Ph. Eur. compliant)	Higher oocyst excretion compared to all four vaccinated groups[a] No difference in weight gain between positive controls and spray on feed vaccinates and drinking water vaccinated groups. Positive control: 100% infected at day 7 PC (Ph. Eur. compliant). 10/10 birds had a lesion score of 3 at day 7 PC.
Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:** Vaccinates	**Results:** Controls
Immunogenicity of E. maxima MCK +10 (EPL 2010-03)						
Negative control (unvaccinated, unchallenged): 20 Positive control (unvaccinated, challenged): 20 Vaccinated1, eye drop: 20 Vaccinated2, spray on feed: 20	SPF	eye drop, spray on feed and spray on chicken at day-old 100 oocysts/dose of *E. maxima* Vaccine strain MCK+10 at X+10 passage level	On D22 Strain *E. maxima* Ingmax $2.0x10^4$ oocysts per bird By oral gavage	6 days post challenge: euthanasia for 10 birds in all three groups 14 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts - Weight gain	Decreased when compared to positive control[a] (Ph. Eur compliant) Growth rate of vaccinated birds	No Pos control less growth than neg

					higher than positive control birds[a] (Ph.	control[a]
Vaccinated3, spray on bird: 20				- Intestinal lesions	Eur compliant) Lesion prevalence of 10% for eye drop, 10% for spray on feed and 60% for spray on bird groups at day 6 PC	Positive control: 90% of birds displayed lesions characteristic of *E. maxima* infection at day 6 PC, however severity of lesions (mean lesion score: 1) was lower than required by Ph. Eur.
Immunogenicity of E. maxima MCK +10 (EPL 2011-07)						
Chickens One day old Negative control (unvaccinated, unchallenged): 21 Positive control (unvaccinated, challenged): 21 Vaccinated1, drinking water: 21 Vaccinated2, spray on feed: 21 Vaccinated3, spray on bird, PBS: 21 Vaccinated4, spray on bird, water: 21	SPF	Drinking water (3 days of age), spray on feed and spray (in PBS and in water as diluent) on chicken (1 day of age) Final product used for vaccination. Test antigen was *E. maxima* MCK+10, at passage level X+11 100 oocysts of *E. maxima* MCK+10 per dose	Day 21 of study (drinking water 18 days PV; spray and eye drop 211 days PV) Strain *E. maxima* Ingmax, $2.0x10^4$ oocysts per bird by oral gavage	6 days post challenge: euthanasia for 10 birds in all three groups 14 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts - Weight gain	No significant differences in oocyst counts compared to positive controls (days 3-14 PC)[b], during second peak (day 34-36) oocyst output was lower than in positive controls[a] (Not compliant with Ph. Eur) Higher in all vaccinated groups than in positive control [a] (Ph. Eur. compliant)	

				- Intestinal lesions	No lesions in any vaccinated bird.	Degree of lesions in positive control birds insufficient. Not compliant with Ph. Eur.
Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:** Vaccinates	**Results:** Controls
Immunogenicity of E. maxima MCK +10 (EPL 2012-04)						
Chickens One day old Positive control (unvaccinated, challenged): 31 Vaccinated1, eye drop :30 Vaccinated2, drinking water: 30	SPF	Eye drop (day-old), spray on feed (day-old), spray on chickens (day-old), drinking water (on D3) Final product used for vaccination. Test antigen *E. maxima* MCK+10) at	Day 21 of study (drinking water 18 days PV; spray and eye drop 21 days PV)) Strain *E. maxima* 103299 Dose of $2.0x10^4$ oocysts per	7 days post challenge: euthanasia for 10 birds in all three groups 14 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts - Weight gain	Decreased when compared to positive control[a] (Ph. Eur. compliant) No difference in	

Vaccinated3, spray on feed:30 Vaccinated4, spray on bird:30		passage level X+10. 100 oocysts/dose	bird	- Intestinal lesions	weight gain compared to positive control[b] (Not compliant with Ph. Eur.) No lesions found in all vaccinated birds (score: zero).	At day 7 PC: 8/10 birds in the positive control group had a score of 2, 2/10 had a score of 1 (Ph. Eur. compliant)
Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:** Vaccinates	**Results:** Controls
Dose Determination for E. mitis (Jormit3+9) (EPL 2008-10)						
Chickens One day old Negative control (unvaccinated, unchallenged): 15 Positive control (unvaccinated, challenged): 15 Vaccinated1, 50 oocysts/ dose of *E. mitis*: 15 Vaccinated2, 150 oocysts/ dose of *E. mitis*: 15 Vaccinated3, 300 oocysts/ dose of *E. mitis*: 15 (Group sizes not Ph. Eur. compliant)	SPF	eye drop (day-old) *E. mitis* strain Jormit3+9. 50 oocyst/dose or 150 oocysts/dose or 300 oocysts/dose	D21 PV Strain *E. mitis* Redmit, 12524 oocysts per dose, by oral gavage	6 days post challenge: euthanasia - Faecal excretion of oocysts - Weight gain - Macrogametocytes and residual oocysts	Oocyst counts were significantly reduced in the 300 oocyst per dose group for day 5 and 6 combined and day 6 PC[a] and in the 150 dose group for day 6 only[a] increased weight gain for all dose groups compared to positive controls[a] (Ph. Eur. compliant) 150 and 300 dose groups showed the greatest reduction in histological macrogametocyte based lesions.	At day 5 PC, faecal oocyst output was similar to all vaccinate groups[b]. At day 6 PC, faecal oocyst output was similar to 50 oocysts/dose vaccinates[b], and higher than 150 and 300 oocyst/dose vaccinates[a] (Not Ph. Eur. compliant) greater across the intestine in the positive control group compared to the 3 vaccinated groups
Dose Confirmation for E. mitis (2009-01)						

Chickens One day old Negative control (unvaccinated and unchallenged) : 20 Positive control (unvaccinated , challend): 20 Vaccinated1, spray on bird: 40	SPF	eye drop, spray on feed and (day-old) spray on chicken (dayold) Final product used for vaccination. Test antigen: *E. mitis* Jormit 3+9 at passage level X+6 at 100 oocysts/dose.	D21 PV (positive control, spray on bird and spray on feed groups) Strain *E. mitis* Redmit, 20,000 oocysts per dose by oral gavage	6 days post challenge: euthanasia for 10 birds in all groups 14 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts	significantly reduced for both spray on feed and spray on chicks groups compared to positive controls[a] (Ph. Eur. compliant)	
Vaccinated2, spray on feed: 20 Vaccinated3, eye drop (vaccinated, not challenged, therefore not included in results): 5				- Weight gain - Gut scrapings: oocysts	better weight gain for both spray on feed and spray on chicks groups than the positive controls[a] (Ph. Eur compliant) Oocysts present in 32% of spray on chickens vaccinates, and in 30% of spray on feed vaccinates	Positive control: 100% showed cycling of oocysts in the gut at day 6 PC. (Ph. Eur. compliant)
Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:** Vaccinates	**Results:** Controls
Immunogenicity of E. mitis (Jormit 3+9) (EPL 2011-15)						

Chickens Positive control (unvaccinated, challengd): 40 Vaccinated, drinking water: 40	SPF	Via drinking water on D3 Final product used for vaccination. Test antigen: *E. mitis* Jormit 3+9 at passage level X+6 at 100 oocysts/dose	D21 PV (D24 of the study) Strain *E. mitis* Redmit, 20,000 oocysts per dose, by oral gavage	6 days post challenge: euthanasia for 10 birds in both groups 21 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts - Weight gain - Gut scrapings: oocysts	reduced when compared to positive controls[a] (Ph. Eur. compliant) only at start of trial (day 24-day 30) weight gain was increased when compared to control[a] (Partially compliant with Ph. Eur.) 10% of vaccinates group showed oocysts in gut scrapings	100% of 12 positive control birds showed the presence of oocysts in faeces (Ph. Eur. compliant) Controls recovered by end of trial, no significant difference in weight gain compared to vaccinates between day 24 and either day 38 or 45[b] 100% of positive controls showed oocyst in gut scrapings day 6 PC (Ph. Eur. compliant)
Immunogenicity of E. tenella Rt3+15 (EPL 2010-05)						
Chickens One day old Negative control (unvaccinated, unchallenged): 20 Positive control (unvaccinated, challenged): 20	SPF	eye drop, spray on feed and spray on chicken at day-old. 150 oocysts/dose of *E. tenella* Rt3+15 at passage level X+8.	D21 PV Strain *E. tenella* Medten, 5000 oocysts per dose by oral gavage	7 days post challenge: euthanasia for 10 birds in both groups 14 days post challenge: euthanasia remaining birds - Faecal excretion of oocysts	Reduced in all vaccinated groups when compared to positive control[a] (Ph. Eur. compliant)	Neg control: 0 Positive control: excretion of oocysts from day 27-35.

Vaccinated1, eye drop: 20 Vaccinated2, spray on feed: 20 Vaccinated 3, spray on chicken: 20				- Weight gain - Lesion scores	not significant when compared to the positive control[b] (Not compliant with Ph. Eur.) mean lesion score of 0 for all vaccinated groups.	Lesions with a score of 2 or higher were present in 100% of positive controls, with a mean lesion score of 2.4 (Ph. Eur. compliant)
Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration dose used**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:** Vaccinates	**Results:** Controls
Immunogenicity of E. tenella Rt 3 +15 (EPL 2011-08)						
Chickens Positive control (unvaccinated, challenged): 44 Vaccinated1, drinking water: 22 Vaccinated2, spray on chick: 44 Vaccinated3, spray on feed: 22	SPF	spray on feed (day-old) and spray on chicken (day old), drinking water (on D3) Final product used for vaccination. Test antigen: *E. tenella* Rt3+15 at passage level X+8, 150 oocysts/dose	D21 of study (spray on feed and spray on chicken: 21 days PV, drinking water: 18 days PV) Strain *E. tenella* Medten, $7.5x10^3$ oocysts per dose, by oral gavage	5 days post challenge: euthanasia for 10 birds in groups 2&3, 20 birds in group 4 14 days post challenge: euthanasia remaining birds - Clinical signs - Lesion scores at 5 days PC - Lesion scores at 14 days PC - Weight gain	No clinical signs (Ph. Eur compliant) Mean lesion score of: 0 spray on feed group 1.5 spray on chick group 1.7 drinking water group 0 (drinking water), 0.2 (spray on feed), 0.25 (spray on chick) Better than control group at day 5 PC[a] (Ph. Eur. compliant)	At day 5 PC, 11 birds were found dead in the positive control group due to severe coccidiosis. Remaining birds were culled due to welfare issues. Severe coccidiosis due to challenge All remaining birds at day 5 were culled, of which 100% showed a lesion score of 3-4 (Ph. Eur. compliant). Chickens were dead before this date due to severe coccidiosis
Immunogenicity of E. tenella Rt3+15 (EPL 2011-17)						

Chickens One day old Positive control (unvaccinated, challenged) 23 Vaccinated1, eye drop: 23 (reduced to 21) Vaccinated2, drinking water: 23 (reduced to	SPF	Eye drop (day-old), spray on feed (day-old) and spray on chickens (day-old), drinking water (on D3) Final product used for vaccination. Test antigen: *E. tenella* Rt3+15 at passage level X+8, 150	D21 of study (drinking water: day 18 PV, for all other vaccianted groups: day 21 PV). Strain *E. tenella* Medten, 5000 oocyst per dose by oral gavage	7 days post challenge: euthanasia for 10 birds 14 days post challenge: euthanasia remaining birds - Oocysts in faeces	Oocyst decreased for all vaccinated groups when compared to positive control at day 3-14 PC[a] (Ph. Eur. compliant)	
21) Vaccinated3, spray on feed: 23 (reduced to 21) Vaccinated4, spray on bird:46 (reduced to 42)		oocysts/dose		- Lesions Weight gain -	Mild to moderate lesion scores at D7 PC of (average) 1.6, 0.5, 0.3 and 1.5; resolved by D14 (Not Ph. Eur. compliant for eye drop and spray on chick) Better for Eyedrop and drinking water groups at D7 PC[a] than positive controls; only eyedrop group at D14 PC better compared to positive control group[a]	Lesion scores > 2: 100% of 10 culled bird at day 7 PC. By day 14 PC 2/10 birds showed evidence of minor lesions.

[a] : significant difference [b] : no significant difference

Dose determination and dose confirmation studies were performed using a suitable number of day-old SPF chicks in groups vaccinated either by eye drop, spray on feed, spray on chicks or in drinking water. An unvaccinated control group was included in each study. All animals were challenged with suitable strains of each species 3 weeks after vaccination. The animals were monitored for clinical signs and oocyst shedding. After challenge infection, the efficacy of the vaccine was demonstrated by reduction of clinical signs, increased weight gain and reduction of oocyst shedding.

The onset of immunity of the HuveGuard MMAT vaccine was demonstrated from 21 days post vaccination. Continued duration of immunity at 42 days in broilers and 9 months in breeders were investigated in additional laboratory studies. Duration of immunity past 21 days after vaccination has not been established:

Animals Groups Number Age	**Antibo dy status**	**Vaccine: route of administrati**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:**

		on dose used				
Study					**Vaccinates**	**Controls**
Duration of Immunity (EPL2012-16A)						
Chickens One day old Vaccinated1, HuveGuard MMAT (d0) and NB (d14): 40 Vaccinated2, HuveGuard M: 40 Vaccinated3, Paracox: 40 Negative control group (unvaccinated, unchallenged): 40 Positive control group (unvaccinated, challenged): 40	Com-mercial coccidiosis free	HuveGuard MMAT, eye drop, one dose in one eye (day-old). HuveGuard NB, eye drop, one dose in one eye (dayold). Paracox-8, drinking water, one application (~0.1 mL per bird) (at 5 days old)	On day 43 *E. acervulina* Ponance (30,000 oocysts per dose) *E. maxima* Ingmax (20,000 oocysts per dose) *E. mitis* Redmit (20,000 oocysts per dose) *E. tenella* Medten (1,000 oocysts per dose) By oral gavage.	7 days postchallenge: half of birds in each group culled 14 days post-challenge: remaining birds are culled. Oocyst count: Weight gain:	During peak oocyst production over days 4-7 PC, both HuveGuard groups showed reduced oocyst output compared to positive controls[a], but over the day 4-14 PC period no significant reduction compared to the positive controls was found[b]. (Not fully compliant with Ph. Eur.) All vaccinated groups	Negative control
				Gut lesion scores:	did not show a weight gain advantage over the positive control group[b]. (Not compliant with Ph. Eur.) HuveGuard MMAT groups: Majority (93% and 84%) had lesion score 0; a single bird had lesion score 2, the remainer had lesion score 1 for *E. acervulina*. Majority (79% and 89%) had lesion score 0, the remainder had lesion score 1 for *E. maxima* All birds had lesion score 0 for *E. tenella*.	birds showed higher weight gain compared to the positive control[a]. Positive control: 100% had a lesion score of 3 for *E. acervulina*, 70% had a lesion score of 2 for *E. maxima* and 25% had a lesion score of 2 for *E. tenealla*. (Ph. Eur. compliant only for *E. acervulina*)
Duration of Immunity (R_H_2012_102)						

Chickens 9 month old broiler breeders Vaccinated, HuveGuard MMAT and ND: 90 Vaccinated, Paracox: 90		Before start of trial: HuveGuard MMAT (day-old, spray on feed) and HuveGuard ND (7 days old, drinking water) Or Paracox (7 day old, drinking water)	At D14 of trial (9 month old hens). (per group 3 animals remaind unchallenged) 15 animals per group were challenged with either: *E. acervulina* and *E. tenella* Or *E. maxima* Or *E. mitis* Or *E. necatrix* Or *E. brunetti*	Day 6 PC: 30 animals per group culled Day 12 PC: 30 animals per group culled. Oocyst count: Gut lesion scores:	One bird died on D21, vaccineunrelated. Total OPG were not different between groups[b]. Total gut lesion scores were higher in the HuveGuard group than in the Paracox group[a]. Odds of presenting lesions associated with *Eimeria* spp. Were not different between groups[b].	No difference in total OPG between infected and uninfected birds[b]. No differences in total gut lesion scores between infected and uninfected birds[b].

[a] : significant difference [b] : no significant difference

No specific studies to investigate the effect of MDA were performed. The applicant provided bibliographical data indicating it is highly unlikely MDA will have an impact on vaccine efficacy.
No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field Trials

The applicant has conducted field studies in order to confirm efficacy of HuveGuard MMAT under field conditions and to evaluate safety. Eleven studies were performed in total, in which 13 flocks in total were vaccinated with HuveGuard MMAT in Belgium, The Netherlands and Germany.

Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration**	**Study design**	**Follow up: Duration Endpoints***	**Results: Cases/total (%)**	
Study					**Vaccinates**	**Controls**

Belgium Broilers One day old T1: Huveguard, 35800 T2: HIPRACOX broilers®, 69000 T3: PARACOX 5, 30000		Spray on birds	Comparison with HIPRACOX © broilers and PARACOX© 5	Max. D42 - Intestinal lesions - Faecal samples - Body weight	No differences overall, but significantly lower on D35 and D40-42 Similar except on D35 and D40-42 where it was lower [b] Higher [b]	
Netherlands Broilers One day old T1: Huveguard, 28000 T2: PARACOX© 5, 25009		Spray on birds	Comparison with PARACOX© 5	Max. D42 - Body weight - Intestinal lesions - Faecal oocysts	Higher at slaughter [b] No significant differences [b] Higher on days 14, 21,35; lower on days 28, 42 [b]	
Netherlands Broilers One day old T1: Huveguard, 35200 T2, PARACOX© 5: 24300		Spray on feed	Comparison with PARACOX© 5	Max. D40 - Body weight - Lesion scores - Faecal oocysts	No significant difference [b] No significant difference [b] Overall higher; higher for *E. acervulina*, *E. tenella*, *E. mitis*, lower for *E. maxima* and *E. necatrix/praecox* and zero in both groups for *E. brunetti* [b]	
Belgium		Spray on	Comparison	Around 6 weeks of		

Broilers One day old T1, Huveguard, 29800 T2: HIPRACOX © broilers, 29800		feed	with HIPRACOX © broilers	age - Body weight - Lesion scores - Faecal oocysts	Significantly higher[a] Significantly lower on D21 and D28; significantly higher on D41/42[a] Overall higher; higher for *E. acervulina*, *E. maxima*, *E. mitis*, *E. necatrix/praecox*, lower for *E. tenella*, and zero in both groups for *E. brunetti* [b]	
Netherlands Broilers One day old T1, Huveguard, 27810 T2, PARACCOX © 5, 25740		Spray on birds	Comparison with PARACOX© 5	D41 - Body weight - Lesion scores - Faecal oocysts	Significantly lower on D7[a] No significant differences [b] Overall lower; higher for *E. maxima*, *E. mitis*, *E. necatrix/praecox*, lower for *E. acervulina* and *E. tenella*, and zero in both groups *for E. brunetti* [b]	
Belgium Broilers One day old T1, Huveguard, 35800 T2: HIPRACOX © broilers, 69800 T3, PARACOX© 5, 30000		Spray on birds	Comparison with HIPRACOX © broilers and PARACOX© 5	D40-42 - Body weight - Lesion scores - Faecal oocysts	No difference at D40-42 [b] No difference overall; significantly lower on D35 and D40-42[a] Higher at the beginning, lower at the end [b]	

Netherlands Broilers One day old T1, Huveguard, 36000 T2:		Spray on feed	Comparison with PARACOX© 5	D40 - Body weight - Lesion scores	No significant difference at D28 and D35 [b] Overall scores significantly higher on	
PARACCOX © 5, 25000				- Faecal oocysts	D21 [a] Overall higher on D7, 14,21,35 and 40; lower on D28 [b]	
Germany Broilers One day old T1, huveguard, 41960 T2, PARACOX© 5, 42300		Spray on feed	Comparison with PARACOX© 5	D42 - Body weight - Lesion scores - Faecal oocysts	Significantly higher[a] No significant differences [b] Higher on D7, 14; lower on D21, 28, 35 [b]	
Belgium Broilers One day old T1, huveguard drinking water, 15930 T2, HIPRACOX © broilers, 29520 T3, Huveguard eye drop, 13680		Eye drop or in drinking water	Comparison with HIPRACOX © broilers	D39 - Body weight - Lesion scores - Faecal oocysts	Significantly lower in both Huveguard groups on D0, 8 and 20[a] Significantly higher on D13 and 20 in both groups[a] Lower for *E. acervulina, E. tenella*, *E. maxima*, higher for *E. mitis* and *E. neactrix/prac ox*, zero in all groups for *E. brunetti* [b]	

Netherlands Broiler breeder One day old T1, Huveguard, 24240 T2, Huveguard, 23976 T3, PARACOX©, 23440 T4, PARACOX©, 24060		Spray on feed or in drinking water	Comparison with PARACOX©; Huveguard groups followed up on D7 or 13 with Huveguard Plus via drinking water	D - Body weight - Lesion scores - Faecal oocysts	No differences [b] No differences overall; significantly higher on D14 and 56; significantly lower on D21 and 28 [a] Peaked at 2 weeks PV	 Peaked at 4 weeks PV

[a] : significant difference [b] : no significant difference

On each trial site at least one house was vaccinated with HuveGuard MMAT and at least one house was vaccinated with Paracox-5 or Hipracox Broilers (positive control). Application routes included spray on birds, spray on feed, drinking water and eye drop. Primary efficacy criteria were Average Daily Gain and Feed Conversion Ratio. Secondary efficacy criteria were mortality, water intake, final weight, Intestinal Lesion Score and Oocyst Per Gram of faeces.
The statistical analysis of primary and secundary efficacy parameters in the field studies revealed no significant differences between flocks vaccinated with HuveGuard MMAT and positive control flocks vaccinated with Hipracox or Paracox. The results of the field studies generally support the efficacy results from the laboratory studies.

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 risk benefit 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 Veterinary Medicines Agencies 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.

Summary of change	**Section updated**	**Approval date**
Increase batch size (NL/V/0206/001/IB/001)	N/A	01 October 2016
Extend the storage for for the *E. mitis* bulk antigen (NL/V/0206/001/II/002)	N/A	19 April 2017
Change in the description of the manufacturing process and deletion of the autoclaving process in the production of saturated salt (NL/V/xxxx/WS/010)	N/A	31 July 20172017
Deletion of eye drops as route of administration and and subsequent changes to the pharmaceutical form and product name (NL/V/xxxx/WS/009)	Module 1 (Name of the veterinary medicinal product)	11 October 2017
Addition of secondary packaging site (NL/V/xxxx/IA/024/G)	N/A	01 November 2017
Change in the name of the sterility and *Campylobacter* testing site (NL/V/xxxx/IA/026/G)	N/A	28 March 2018
Addition of site for batch release sterility testing, removal *Campylobacter* batch release test and inclusion of Rapid Potency Test as an alternative test for the end of shelf life potency (NL/V/0206/II/007/G)	Module 3, section II.E	04 March 2020