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 NB

Created: July 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0207/001/MR
Name, strength and pharmaceutical form	HuveGuard NB suspension for oral suspension
Applicant	Huvepharma NV Uitbreidingstraat 80 2650 Antwerp Belgium
Active substance(s)	Oocysts of precocious strains of coccidia species: - *Eimeria brunetti* - *Eimeria necatrix*
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. necatrix* and, *E. brunetti.*

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	28 April 2016
Date product first authorised in the Reference Member State (MRP only)	15 July 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 quantity of 100 sporulated oocysts of *Eimeria necatrix strain* mednec$_{3+8}$ and a minimum quantity of 50 sporulated oocysts of *Eimeria brunetti* strain roybru$_{3+28}$ during the shelf life. The excipients are: polysorbate 80, sodium chloride, potassium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate 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 of 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

The active substances are sporulated oocysts of *Eimeria necatrix* strain mednec$_{3+8}$ and *Eimeria brunetti* strain roybru$_{3+28}$. 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, and 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 reconstituted vaccine is supported by the data provided.

G. Other Information

None.

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III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of an overdose administration in the target animal is demonstrated in a study where a ten-fold overdose was administered via eye drop in 15 day-old chicks and 14-day-old birds using HuveGuard NB batch E2P140442 and E2P140781, respectively. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The vaccine was found to be safe (at ten times the maximum release titre) as no vaccinated chicks showed notable signs of coccidiosis or died from causes attributable to the vaccine. 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.

No studies towards the immunological functions have been performed. Based on a study performed with HuveGuard MMAT (NL/V/0206/001/MR), it may however be assumed that this product will not adversely affect the immune system of the vaccinated animal or its progeny, therefore a specific study was not carried out.

For each live strain included in the vaccine specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment. *E. necatrix* and *E. brunetti* showed no indication of a change in virulence.

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

The safety of the product has been monitored in 6 field trials. The product has been tested under field conditions in The Netherlands, Belgium and France. Different routes of administration (drinking water, eye drop, spray on birds) have been investigated in these trials. The efficacy and safety of HuveGuard NB under field conditions has been investigated following a vaccination with HuveGuard NB and HuveGuard MMAT. Results of the field studies generally conform the safety profile as established in the laboratory studies.

User Safety

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.

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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.

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Huvepharma NV	MRP
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IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements. Tests for immunogenicity of the *E. necatrix* mednec$_{3+8}$ and *E. brunetti* (roybru$_{3+28}$) antigens within HuveGuard NB vaccine and dose determination (immunogenicity) of *E. brunetti* (roybru$_{3+28}$) single antigen are described below:.

Animals Groups Number Age	**Antibody status**	**Vaccine, dose, route of administration**	**Challenge, dose, Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:**	
Study					**Vaccinates**	**Controls**
Dose Confirmation *E. necatrix* (single antigen) (EPL2011-02)						
Chickens One day old Negative control (unvaccinated, unchallenged): 20 Positive control (unvaccinated, challenged): 20 Vaccinated1, spray on bird: 20 Vaccinated2, spray on feed: 20	SPF	Spray on feed (day-old), spray on chickens (day-old) *E. necatrix* (mednec 3+8) at passage level X+8, 100 oocysts/dose	D21 of the study (21 days PV) Strain *E. necatrix* Gronec, 2.5 x 10^3 oocysts per bird by oral gavage	7 days post challenge (PC): euthanasia for 10 birds in all groups 14 days post challenge: euthanasia remaining birds - Body weight - Faecal oocysts - Intestinal lesions	Only higher than the positive control for the spray on chicks group for day 0-7 PC[a]. Both vaccinated groups had a lower OPG for day 6-8 PC than the positive control group[a] (Ph. Eur. compliant) Significantly lower for both vaccinate groups compared to positive control at day 7 PC[a], although mean lesion scores were 1.2 and 1.4 for spray on bird and spray on feed, respectively (Not Ph. Eur. compliant).	Negative control group had a higher weight gain than positive control group[a]. 90% of positive control birds at day 7 PC had a lesion score of 2 or 3, with a mean lesion score of 2.1 (Ph. Eur. compliant)
Dose Determination *E. brunetti* (single antigen) (EPL2010-01)						
Chickens 14 days old Negative control (unvaccinated, unchallenged): 19	Hy-Line brown male (not SPF)	Eye drop (14 days old) *E. brunetti* Roybru 3+28 Dose: 50 oocysts Or 100 oocysts	21 days PV Strain *E. brunetti* (AM), 10,000 oocysts per dose by oral gavage	7 days post challenge: euthanasia for 10 birds in all groups 14 days post challenge: euthanasia remaining birds		

Positive control (unvaccinated, challenged): 20 Vaccinated1, 50 oocysts/dose: 20 Vaccinated2, 100 oocysts/dose: 20 Vaccinated3, 200 oocysts/dose: 20		Or 200 oocysts		- Body weight - Faecal oocysts - Intestinal lesions	All 3 vaccinated groups were heavier than the positive control group on both day 7 and 14 PC[a]. (Ph. Eur. compliant) No faecal oocyst output after challenge in any of the 3 vaccinated groups No lesions (score of 0 for 100% of the birds) in all 3 vaccinated groups. (Ph. Eur. compliant)	Negative controls higher weight gain than positive controls[a]. Significantly higher in positive control when compared to vaccinates[a] (Ph. Eur. compliant) Positive control: score ≥2 in 70% at 7 days PC; no lesions at day 14 PC (Not Ph. Eur. compliant)
Dose Confirmation (immunogenicity) E. brunetti in the HuveGuard® NB product (EPL2011-03)						
Chickens 14 days old Negative control (unvaccinated, unchallenged): 22 Positive control (unvaccinated, challenged): 22 Vaccinated1, eye drop: 22 Vaccinated2, drinking water: 22	SPF	Eye drop (14 day-old) and drinking water (14 day-old) HuveGuard NB Test antigen: *E. brunetti* Roybru 3+28, 50 oocysts per dose	Day 21 PV Strain *E. brunetti* (AM) 10,000 oocysts per dose by oral gavage	7 days post challenge: euthanasia for 12 birds in all groups 15 days post challenge: euthanasia remaining birds - Body weight - Faecal oocysts - Intestinal lesions	1 bird from the drinking water group died (not vaccine related) Significantly higher for both vaccinated groups compared to the positive controls[a] (Ph. Eur. compliant) Significantly reduced for both vaccinated groups compared to the positive control[a] (Ph. Eur. compliant) 100% of vaccinated birds had a lesion score of 0 on day 7 and day 15 PC, which was different from the positive controls[a]. (Ph. Eur. compliant)	On day 7 PC 100% of positive control birds had a lesion score of 2 (Ph. Eur. compliant)

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

The data provided on pivotal laboratory efficacy trials of HuveGuard NB vaccine against *E. necatrix* and *E. brunetti* in SPF chicks are satisfactory and in accordance with the requirements of specific Ph.Eur. monograph 2326 for this type of vaccine.

During a post-authorisation variation, additional laboratory studies were provided supporting the administration of the vaccine from 1 day of age when administered via spray on feed or spray on birds, and from 3 days of age when administered via the drinking water. Two post-authorisation laboratory trials were submitted, and these are summarized below.

Animals Groups Number Age	**Antibody status**	**Vaccine, dose, route of administration**	**Study design**	**Follow up: Duration Endpoints***	**Results:**	
Study					**Vaccinates**	**Controls**
Immunogenicity of HuveGuard NB by spray on bird, spray on feed, drinking water (EPL 2018-09)						
219 Chickens, Mixed gender 1 Day-old positive control (unvaccinated, challenged): Part A ≥ 20 Part B ≥ 20 2 Spray on birds vaccinated: Part A ≥ 20 Part B ≥ 20 3 Spray on feed vaccinated: Part A ≥ 20 Part B ≥ 20 4 3-day-old positive control (unvaccinated, challenged): Part A ≥ 20 Part B ≥ 20 5 Drinking water vaccinated: Part A ≥ 20 Part B ≥ 20	SPF	HuveGuard NB (vaccination in day-old birds via spray on birds or spray on feed and in 3-day-old birds via drinking water)	Part A: challenge with *E. necatrix* at 21 days old for group 1-3 and at 24 days old for group 4-5. Part B: challenge with *E. brunetti* at 21 days old for group 1-3 and at 24 days old for group 4-5.	Day 7, 14, 21 post vaccination and day 2, 5, 7, 8, 11, 14 post challenge - Body weight - Lesion score - Faecal oocysts	Part A *E. necatrix*: Significantly greater weight gain for the drinking water vaccinated group on day 7 PC compared to positive control[a] (Ph. Eur. compliant), spray on bird and spray on feed not different[b] (not Ph. Eur. compliant) Part B *E. brunetti*: all 3 vaccinated groups showed greater weight gain compared to positive control at day 7 and 14 PC[a] (Ph. Eur. compliant) Part A *E. necatrix*: All 3 vaccinated groups had reduced lesion scores compared to the positive controls on day 7 PC[a] (Ph. Eur. compliant). Part B *E. brunetti:* All 3 vaccinated groups had reduced lesion scores compared to the positive controls on day 7 PC[a] (Ph. Eur. compliant). Part A *E. necatrix*: the 3 vaccinated groups showed oocyst cycling with the peak on day 7 PV. Total oocysts output from days 3-14 PC was lower for all 3	. Both control groups remained free from oocysts for study part A and B.

					vaccinated groups compared to the control groups[a] (Ph. Eur. compliant). Part B *E. brunetti*: the drinking water and spray on bird vaccinated groups showed oocyst cycling with the peak on day 7 PV, the spray on feed group only had oocysts observed on day 21 PV. Total oocyst output from days 3-14 PC was lower for spray on bird and drinking water vaccinates compared to the control groups[a] (Ph. Eur. compliant), the spray on feed group failed to show protection[b] (not Ph. Eur. compliant).	
Assessing the efficacy of HuveGuard® NB vaccine sprayed on birds in protecting chickens against the challenge with Eimeria necatrix and Eimeria brunetti (P19162-ISO)						
Chicken, male and female 1 positive control (unvaccinated, challenged with *E. necatrix*): 26 birds 2 positive control (unvaccinated, challenged with *E. brunetti*): 26 birds 3 test group (vaccinated, challenged with *E. necatrix*: 26 birds 4 test groep (vaccinated, challenged with *E. brunetti*): 26 birds	SPF	Group 3 and 4: HuveGuard NB (vaccination in day-old birds via spray on birds)	Oocyst counting and lesion scoring was blinded. Challenge on day 20: all groups were inoculated orally with challenge strains of *E. acervulina* combined with either *E. necatrix* or *E. brunetti*	Study day 7, 14, 20, 25, 26, 27, 28, 31, 34. - Body weight - Lesion score	During the acute phase of infection (day 20-26) both vaccinated groups had higher weight gain compared to their respective control groups[a]. For the groups challenged with *E. brunetti*, overall weigh gain (day 20-34) was also higher in the vaccinated group[a] (Ph. Eur. compliant). On day 26 and 27, a reduction in lesion score was observed for *E. necatrix* for the vaccinated group 3 (mean score: 0) compared to its positive control (mean score: 1.5)[a] (Ph. Eur. compliant). In both groups challenged with *E. brunetti*, no lesions were observed[b] (Not Ph. Eur. compliant).	

				- Faecal oocysts	On day 7, 14 and 20 oocyst cycling is observed in vaccinated groups (Ph. Eur. compliant). OPG countings on day 25, 28, 31 and 34 showed a high shedding pattern for *E. acervulina* and only minor OPG countings for *E. brunetti* and *E. nectatrix* and was therefore inconclusive (Not Ph. Eur. compliant).	On day 7, 14 and 20 the OPG of unvaccinated controls is 0 (Ph. Eur. compliant)

Duration of immunity at 9 months was investigated in broiler breeding hens, Ross 308 of 9 months old.

Animals Groups Number Age	**Antibody status**	**Vaccine, dose, route of administration**	**Challenge, dose, Day post-vaccination**	**Follow up: Duration Endpoints***	**Results:**	
Study					**Vaccinates**	**Controls**
Assessment of the duration of the immunity of HuveGuard MMAT and HuveGuard NB in breeders (R-Huvepharma-2012-102)						
Chickens Broiler breeding hens 9 months old Vaccinated1, Huveguard MMAT and NB: 90 Vaccinated2, PARACOX-8©: 90	Com-mercial	Before start of trial: HuveGuard MMAT (day-old, spray on feed) and HuveGuard NB (7 days old, drinking water) Or Paracox (7 day old, drinking water)	At day 14 of trial (9 month old hens). (per group 3 animals remained 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, vaccine-unrelated. 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

There were no significant differences between HuveGuard NB and positive control groups for total lesion scores and *E. brunetti* and *E. necatrix* OPGs. Nevertheless, duration of immunity past 21 days after vaccination has not been established.

Field Trials

Initially the applicant conducted 6 field studies. In total, 9 flocks been have vaccinated with HuveGuard NB. All studies have been executed in accordance with the same protocol. On each trial site, at least one house has been vaccinated with HuveGuard NB and at least one house has been vaccinated with a positive control vaccine. Different routes of administration

have been investigated: 6 flocks were vaccinated via drinking water, 2 flocks were vaccinated via eye drop, 1 flock was vaccinated by spray on chick (supportive evidence only). In the field studies birds were vaccinated at ages between 7 and 14 days. The results of the 6 studies have been statistically analysed for each study separately and a meta-analysis has been performed for 3 studies to confirm efficacy when administered via the proposed routes of application.

Animals Groups Number Age	**Antibody status**	**Vaccine, dose, route of administration**	**Study design**	**Follow up: Duration Endpoints***	**Results:**	
Study					**Vaccinates**	**Controls**
R-Huvepharma-2011-54 Netherlands Chickens Broiler breeder Day-old Vaccinated1, HuveGuard MMAT + HuveGuard NB: 48216 Vaccinated2, PARACOX-8©: 47500		HuveGuard MMAT (spray on feed, day old) and HuveGuard NB (drinking water, 7 or 13 days old) Or Paracox (drinking water, 6 or 7 days old)	Comparison with PARACOX©	5 animals of the 4 houses used were euthanized on days 7, 14, 21, 28, 35, 56 and 84. Trial ended at day 140 (last animals moved to production farm) - Body weight - Intestinal lesions - Faecal oocysts	No difference between groups No differences overall; significantly higher on D14 and 56; significantly lower on D21 and 28 [a] Peak at around 2 weeks PV	Significantly higher on D21 and D28[a] Peak at around 4 weeks of age
R-Huvepharma-2011-55 Belgium Chickens Broiler breeder Day-old Vaccinated1, Huveguard MMAT + HuveGuard NB: 13898 Vaccinated2: PARACOX-8©: 13342		HuveGuard MMAT (spray on feed, day old) and HuveGuard NB (eye drop, 9 days old) Or Paracox (drinking water, 7 days old)	Comparison with PARACOX©	5 animals per house were euthanized on days 7, 14, 21, 28, 35, 56 and 84 - Body weight - Lesion scores - Faecal oocysts	Significantly higher in the HuveGuard group at all timepoints except at day 0[a] No scores above 1 in both groups; significantly higher ILS scores on D35 in the HuveGuard group[a] Similar patterns in both groups[b]	Control group was heavier at the start of the study[a] No scores above 1 in both groups; Significantly higher ILS scores on D56 in the control groups[a]
R-Huvepharma-2011-96 France Chickens		HuveGuard MMAT (spray on feed, day old) and	Comparison with PARACOX©	5 birds/group were euthanized on D7, 14, 21, 28, 35, 56 and 84		

Newly hatched Broiler breeders Vaccinated1, Huveguard MMAT and HuveGuard NB: 18760 Vaccinated2, PARACOX-8©: 19720		HuveGuard NB (drinking water, 7 or 14 days old) Or Paracox 8 (drinking water, 7 days old)		- Body weight - Intestinal lesions - Faecal oocysts	No difference between the groups[b] No difference between the groups[b] Different OPG patterns between groups. Higher peak at the age of 2-3 weeks in the HuveGuard groups	Small peaks which were decreasing towards the end of the rearing period for the control group.
R-Huvepharma-2012-11 Belgium Broiler breeders Vaccinated 1, HuveGuard MMAT and HuveGuard NB: 9722 Vaccinated2, PARACOX-8©: 10000		HuveGuard MMAT (drinking water, 4 days old) and HuveGuard NB (drinking water, 9 days old) Or Paracox (drinking water, 9 days old)	Comparison with PARACOX©	5 birds/group were euthanized on D6, 13, 20, 27, 34, 55, 83 and 131 - Body weight - Intestinal lesions - Faecal oocysts	Higher at D83[a]. Over whole study period not difference in daily weight gain[b] Higher on D13 an D20[a] in the HuveGuard group, although still below ILS score 1 Different OPG patterns between groups. Consecutive small peaks which were decreasing towards the end of the rearing period	Higher in D20 and D27[a]. Over whole study period not difference in daily weight gain[b] Higher on 83[b] Different OPG patterns between groups. Two high peaks at the age of 41 and 83 days
R-Huvepharma-2012-74 Belgium Chickens Rearing pullets Vaccinated1, HuveGuard MMAT and HuveGuard NB: 45015 Vaccinated2, PARACOX-8©: 20260		HuveGuard MMAT (eye drop, day-old) and HuveGuard NB (spray on birds, 7 days old) Or Paracox (drinking water, 7 days old)	Comparison with PARACOX©	5 birds/group on D8, 15, 22, 29, 36, 57 and 85 - Body weight - Intestinal lesions - Faecal oocysts	Significantly higher on Day 0, 85 and 119 for HuveGuard group compared to control[a] Significantly higher on D85 for Huveguard group compared to control[a] Similar OPG pattern in both groups, peak at around age of 7-8 weeks	
R-Huvepharma-2012-75 Belgium		HuveGuard MMAT (spray on birds or eye drop, day-old) and		5 birds/group on D7, 14, 21, 28, 35, 56 and 85 - Body weight		

Chickens Rearing pullets – bio layers Vaccinated1, Huveguard: 14430 Vaccinated2, PARACOX-8©: 12726		HuveGuard NB (eye drop or drinking water, 7 days old) Or Paracox (drinking water, 9 days old)		- Intestinal lesions - Faecal oocysts	Significantly higher in D85[a], although no difference at the end of the study compared to control[b] Different OPG patterns between groups. Peaks appeared at younger age (2 weeks and 7 weeks) and were higher	Significantly higher on D28 and D56[a] Higher on D14 and D28, D35, D56 in the control group[a] Different OPG patterns between groups. Lower peaks at age of 3, 7 and 10 weeks

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

The efficacy is confirmed by appropriate performance parameters in field trials in Europe in breeder chickens. Based on the efficacy data above, the vaccine is considered to be suitable for the active immunisation of chickens from 14 days of age to reduce infection and clinical signs of coccidiosis caused *by E. necatrix and E. brunetti* with an Onset of Immunity at 21 days post vaccination.

During a post-authorisation variation, additional field studies were provided supporting the administration of the vaccine from 1 day of age when administered via spray on feed or spray on birds, and from 3 days of age when administered via the drinking water. These post-authorisation field trials are summarized below.

Animals Groups Number Age	**Antibody status**	**Vaccine, dose, route of administration**	**Study design**	**Follow up: Duration Endpoints***	**Results:**	
Study					**Vaccinates**	**Controls**
Efficacy and Safety of HuveGuard NB under commercial conditions when applied at first day of age by course spray (R-Huvepharma-2016-12)						
Chickens, females, Ross 308 House 1 (positive control): 9484 birds House 2 (test group): 8862 birds		House 1 (positive control): day-old chicks vaccinated on day 0 with HuveGuard MMAT (spray on bird) and on day 14 (15 day old) with HuveGuard NB (via drinking water). House 2: day-old chicks vaccinated on day 0 with HuveGuard MMAT and	Controlled, non-blinded study (oocyst counting and differenciation was blinded) Field study	Study days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 118, 126 and 136 - Faecal oocysts - Lesion scores	No differences were detected in OPG between the houses for all *Eimeria* species in the vaccine[b]. No differences in total mean lesion score were observed between the groups[b]. No differences were detected in species specific lesion scores[b].	

		HuveGuard NB (both: course spray on bird).		- Body weight	At D0 and D84 birds that were vaccinated with HuveGuard NB on day 0 (house 2) weighed more[a], on other test days there was no difference[b].	
Efficacy and Safety of HuveGuard NB under commercial conditions when applied at first day of age by course spray on feed (R-huvepharma-2016-37)						
Chickens, females, Ross 308 House 1 (positive control):24,500 birds House 2 (test group): 11,200 birds		House 1 (positive control): 8 days old chicks vaccinated (on study day 7) with Paracox® 8 via drinking water. House 2: day-old chicks vaccinated on day 0 (arrival on farm) with HuveGuard MMAT and HuveGuard NB (both: course spray on feed).	Controlled, non-blinded study (oocyst counting and differentiation was blinded) Field study	Study days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 118, 126 and 136 - Faecal oocysts - Lesion scores - Body weight	No differences in total or species-specific OPG between houses[b]. The HuveGuard group had a higher total lesion score on day 14 (2.8 vs. 1.4) and day 56 (1.8 vs. 0.4)[a]. On day 28, the HuveGuard group had a significantly lower total lesion score (1.6 vs. 3.8)[a]. There was no difference in lesion score on day 7, 21, 35,and 85. Species specific lesion scoring was only different for *E. tenella* (higher score for HuveGuard group)[a]. At the start of the study birds from the HuveGuard group weight less[a]. At day 56, 85, and 135 no difference in weight was observed[b].	
Efficacy and Safety of HuveGuard NB under commercial conditions when applied at first day of age by course spray (R-Huvepharma-2016-83)						
Chickens, H&N Super Nick, H&N Nick Chick, H&N Brown Nick, LB Classic House1 (positive control): 85,649 animals House 2 (test group): 63,240 animals		House 1 (positive control) treatment 1: Paracox® 8 via spray on birds at 1 day of age in the hatchery House 1 (positive control) treatment 2: Evalon® via	Controlled, non-blinded study (oocyst counting and differentiation was blinded) Field study	Study days 7, 14, 21, 28, 35, 42, 49, 56/57, 63, 70, 77, 84, 91, 98, 105, 112, 116 and 119. - Faecal oocysts	Total and species specific oocyst shedding was not different between houses[b].	

		spray on birds at 1 day of age in the hatchery House 2 (test group): HuveGuard MMAT and HuveGuard NB via spray on birds at 1 day of age in the hatchery		- Lesion scores - Body weight	No differences were observed in lesion scores for all study days. *E. acervulina* lesion scores were lowest for Evalon® vaccinated birds[a]. At set-up and day 28, bird vaccinated with HuveGuard weighed less than birs from house 1[a]. At day 116 birds vaccinated with HuveGuard were heavier than birds from house 1[a].	
Efficacy of HuveGuard® NB in controlling coccidiosis in slow growing broilers under field conditions in Belgium (R-Huvepharma-2018-130a)						
Chickens, Sasso broilers. House 1 (test group): 5000 birds House 2 (vaccinated positive control): 5000 birds		House 1: vaccinated at day of arrival on study site (day-old) with HuveGuard MMAT and HuveGuard NB via spray on birds. House 2 (control): vaccinated on day of arrival on study site (day-old) with Paracox® via spray on birds.	Controlled, non-blinded trial (oocyst counting and differentiation was blinded) Field study	Study days 0, 7, 14, 21, 28, 35, 56 and 70. Slaughter after 70 days. - Faecal oocysts - Lesion score - Body weight	No statistical analysis performed. No differences in total intestinal lesion scores were observed between the HuveGuard group and the control group[b]. No difference in weight gain between the HuveGuard groups and the control group[b].	
Efficacy of HuveGuard® NB in controlling coccidiosis in slow growing broilers under field conditions in Belgium (R-Huvepharma-2018-130b)						
Chickens, Sasso broilers. House 1 (test group): 5035 birds House 2 (vaccinated positive control): 5035 birds		House 1: vaccinated at day of arrival on study site (day-old) with HuveGuard MMAT and HuveGuard NB via spray on feed. House 2 (control): vaccinated on day of arrival on study site (day-old) with Paracox® via spray on feed.	Controlled, non-blinded trial (oocyst counting and differentiation was blinded) Field study	Study days 0, 7, 14, 21, 28, 35, 56 and 70. Slaughter after 70 days. - Faecal oocysts - Lesion score - Body weight	No statistical analysis performed. No differences in total intestinal lesion scores wer observed between the HuveGuard group and the control group[b]. No difference in bird weight between the HuveGuard groups and the control groupb.	
Efficacy of HuveGuard® NB in controlling coccidiosis in slow growing broilers under field conditions in Belgium (R-Huvepharma-2018-130c)						

Chickens, Sasso broilers. House 1 (test group): 4955 birds House 2 (vaccinated positive control): 5000 birds		House 1: vaccinated at 5 days of age with HuveGuard MMAT and HuveGuard NB via drinking water. House 2 (control): vaccinated on day of arrival on study site (day-old) with Paracox® via spray on birds.	Controlled, non-blinded trial (oocyst counting and differentiation was blinded) Field study	Study days 0, 5/6, 14, 21, 28, 35, 56 and 70. Slaughter after 70 days. - Faecal oocysts - Lesion score - Body weight	No statistical analysis performed. No differences in total intestinal lesion scores wer observed between the HuveGuard group and the control group[b]. Bird body weight was lower for the HuveGuard group (mean 1,358 kg) compared to the control group (mean 1,423 kg)[a].	

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

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/0207/001/IB/002)	N/A	01 October 2016
Change in rapid potency test: from testing in day-old SPF chicks to testing in 1-14 days old SPF chicks (NL/V/0207/001/II/001)		07 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 2017
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
Reduction minimum age for vaccination to 1 day of age for administration via spray onto feed or spray on birds and to 3 days of age for administration via drinking water (NL/V/0207/001/II/007)	Module 3, section IV	27 November 2019
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/0207/II/008/G)	Module 3, section II.E	13 March 2020