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PUBLICLY AVAILABLE ASSESSMENT REPORT FOR AN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCT

CEVAC MEGAMUNE K

MODULE 1

PRODUCT SUMMARY

Procedure number	15429
Name and pharmaceutical form	CEVAC MEGAMUNE K emulsion for injection
Applicant	CEVA Santé Animale
Active substance(s)	Each dose of 0.5 ml vaccine contains : Inactivated Newcastle disease virus, strain NDV-SZ LaSota Inactivated avian infectious bronchitis virus, strain M-41 Inactivated avian infectious bronchitis virus, strain QXFr Inactivated egg drop syndrome virus, strain B8/78 Inactivated avian metapneumovirus, strain TRT50
ATC Vetcode	QI01AA18
Target species	Chickens
Indication for use	Cevac Megamune K is recommended for the vaccination of layer and breeder type chicken flocks, in order - to reduce mortality, clinical signs and lesions caused by Newcastle disease virus; - to reduce egg drop, respiratory signs and virus shedding caused by the Massachusetts and QX-like serotypes of Infectious bronchitis virus; - to reduce egg drop caused by the Egg drop syndrome virus; - to reduce respiratory signs and virus shedding caused by Avian metapneumovirus.

MODULE 2

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this immunological veterinary medicinal product (IVMP) are available in the Union Product Database (UPD).

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

SUMMARY OF ASSESSMENT

Legal basis of original application	application in accordance with Article 8 of Regulation (EC) 2019/6 as amended.
Date of completion of the original procedure	
Date immunological veterinary medicinal product first authorised in the Reference Member State (MRP only)	
Concerned Member States (CMS) for original procedure	-

1. SCIENTIFIC OVERVIEW

CEVAC MEGAMUNE is an inactivated vaccine which is indicated in chickens from 14 weeks of age against Newcastle disease (to reduce mortality, clinical signs and lesions) and infectious bronchitis linked to serotypes Massachusetts and QX (to reduce egg drop, respiratory signs and viral shedding), egg drop syndrome (to reduce egg drop) avian metapneumovirus (to reduce clinical signs and virus shedding). The vaccine contains paraffin as adjuvant. Thiomersal is added as preservative. The vaccine is presented as emulsion for injection in multidose containers with a respective dose volume of 0.5 ml. For infectious bronchitis and avian pneumovirus, the vaccine should be used in chickens previously vaccinated with relevant live vaccines.

The product is manufactured and controlled using validated methods and tests that ensure the consistency of the product released on the market.

It has been shown that the vaccine can be safely used in the target species ; the slight reactions observed after vaccination – injection site reddening disappearing within 1 day - are indicated in the SPC.

The IVMP is also 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 IVMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

2.A. Product description

Each dose of 0.5 mL vaccine contains :

ingredient	quantity
Newcastle disease virus strain “SZ” La Sota, inactivated	≥ 18.6 EU[1]
Avian infectious disease virus strain M41, inactivated	≥ 5.3 log_2 HI titre[2]
Avian infectious disease virus strain QX Fr, inactivated	≥ 18.6 AU[3]
Egg drop syndrome virus strain B8/78, inactivated	≥ 8.0 log_2 HI titre
Avian metapneumovirus, strain TRT50, inactivated	≥ 26.4 EU
adjuvant	
Paraffin, light liquid	0.27 mL
Excipients	
Sorbitan oleate	
Polysorbate 80	
Thiomersal	
PBS solution	Ad 0.5 ml

[1] EU - antigen ELISA unit
[2] HI – haemagglutination inhibition
[3] AU – antibody ELISA unit

The emulsion is filled in low density polyethylene bottles of 100 mL or 500 ml, closed with nitrile rubber stoppers and aluminium/plastic caps. The particulars of the containers and controls performed are provided and conform to regulation.

The choice of the vaccine strains and formulation of the vaccine are justified.

Development of the vaccine is adequately described in accordance with the relevant European guidelines.

2.B. Description of the manufacturing method

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

Process validation data on the product are provided in accordance with the relevant European guidelines.

The product is manufactured in accordance with the European Pharmacopoeia (Ph. Eur.) and relevant European guidelines.

The inactivation processes and the detection limits of the control of inactivation for each active substance are correctly validated.

2.C. Production and control of starting materials

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs where these exist, or in-house specifications.

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. 5.2.5.

The master and working seeds were produced according to the seed lot system as described in the relevant guideline(s).

Scientific data and/or certificates of suitability issued by the EDQM are provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products was satisfactorily demonstrated.

2.D. Control tests during the manufacturing process

In-process control tests are carried out on intermediate stages of manufacture in order to verify the consistency of the manufacturing process and the final product.

The tests performed during production are described, validated when relevant and the results of three consecutive runs, conforming to the specifications, are provided.

2.E. Control tests on the finished product

The tests performed on the finished product and their specifications are justified and are considered appropriate to adequately control the quality of the product.

They include :

- Appearance,
- Filling volume
- Physico-chemical control (emulsion, viscosity, stability of emulsion, free formaldehyde, thiomersal)
- Sterility
- Identification and potency of each active substance

Satisfactory validation data for each analytical methods are provided, if appropriate.

The tests performed on the final product conform to the relevant requirements and monographs, if applicable; any deviation from these requirements is justified. They allow to guarantee safety and efficacy of the released vaccines.

2.F. Batch-to-batch consistency

Full protocols of 4 consecutive batches of the product, representative of the routine production and giving the results for all tests performed during production and on the finished product, are provided in order to ensure that quality is consistent from batch to batch and to demonstrate conformity with the predefined specifications.

.G. Stability tests

Stability data on the active substance(s) are provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored by the applicant under the approved conditions.

Stability data on the finished product are provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (12 months) when stored under the approved conditions (at 2-8°C).

The in-use shelf life of 10 hours of the broached vaccine is supported by the data provided. The recommendations in the product leaflet should be followed.

3. SAFETY DOCUMENTATION (safety and residues tests)

3.A. General requirements

The vaccine should be given from 14 weeks of age but not later than 3 weeks before the expected onset of laying period. It should be administered as 0.5 ml dose by intramuscular route.

The safety of the IVMP when administered to the target species, the potential harmful effects (residues in IVMP, substance in foodstuff), the potential serious risk for human beings during product administration and to the environment are adequately described.

The studies were performed according to the recommendations of Regulation (EU) 2019/6, relevant guidelines or Ph. Eur. when applicable.

All pre-clinical studies were completed according to the principles of Good laboratory Practice.

Vaccine batches used in the studies were produced and controlled according to quality part.

3.B. Pre-clinical studies

The safety of the administration of one dose to the chickens was demonstrated.

Study aim	Safety study
Animals and application scheme (study groups)	30 chickens 14 weeks old vaccinated as recommended and 30 controls receiving placebo.
Follow-up	Daily observation during 21 days including body weighing, visual inspection and palpation of the injection site and histopathological examination of tissues from vaccination site after 14 or 21 days
Results	Absence of any adverse reactions – local reactions as slight reddish discoloration for 1 day and necropsy findings in accordance with administration of an oil adjuvanted vaccine
Conclusion	Vaccination is safe

CEVAC MEGAMUNE is an inactivated vaccine. There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny. Therefore, no specific study was carried out.

The vaccine contains only inactivated antigens and, thus, the specific tests to be performed for live vaccines are not applicable.

No information is available on the safety of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

As the vaccine contains mineral oil, a warning to the user and to the physician is included in the SPC (Summary of Product Characteristics).

Overall, the vaccine proved to be well tolerated in chickens. The local reactions that may be observed after vaccination (injection site reddening red during at most 1 day) are described in the SPC and package leaflet.

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CEVA	National
Publicly available assessment report	

3.C. Clinical trials

2 clinical studies were conducted to evaluate safety of the vaccine.

Studies aim	Safety of the vaccination
Animals and application scheme (study groups)	17 week old commercial layers in 2 locations 61530 layers were vaccinated with 1 dose of vaccine and a 2nd group received a comparator vaccine
Follow-up	Daily clinical examination – recording of weight, feed consumption, egg production – necropsy of 10 birds after 3 weeks, 13 weeks and 43 weeks
Results	Absence of any adverse reactions after vaccination – no differences between the groups for body weight, feed consumption and egg production and quality – all observations within expected ranges – no pathological findings at necropsy and adverse lesions
Conclusion	Vaccination is safe among field conditions.

3.D. 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 in the product literature are adequate to ensure safety to the environment when the product is used as directed.

3.F. Residue tests to be included in the pre-clinical studies

The adjuvant components (paraffin) and all excipients used are considered to be safe because they are mentioned in Table 1 of Commission regulation 37/2010 requiring no MRL insert status with reference to MRL regulations. Antibiotics used during production of the vaccine will be present only as traces. Based on this information, no withdrawal period is proposed.

4. EFFICACY DOCUMENTATION

4.A. General requirements

The vaccine should be given from 14 weeks of age but not later than 3 weeks before the expected onset of laying period. It should be administered as 0.5 ml dose by intramuscular route.

The studies were performed according to the recommendations of Regulation (EU) 2019/6, relevant guidelines or Ph. Eur. when applicable.

All pre-clinical studies were completed according to the principles of Good laboratory Practice.

Vaccine batches used in the studies were produced and controlled according to quality part.

4.B. Pre-Clinical Studies

The efficacy of the product was demonstrated in laboratory studies under well-controlled conditions in accordance with the relevant requirements.

Efficacy of the ND component

Study aim	immunogenicity
vaccine	CEVAC MEGAMUNE K administered by IM route
Animals and application scheme (study groups)	SPF chickens, 4 weeks old Vaccinates: 32 chickens receiving 1/25 vaccine dose / 32 receiving 1/50 vaccine dose and 32 receiving 1/100 dose Controls: 15 chickens
Challenge	21 days after vaccination, challenge with virulent strain Herts 33/56 of NDV
Follow up / evaluation criteria*	During 21 days investigation of ND specific signs and serological testing on day 21 (inhibition of hemagglutination)
Results	Rates of protection were 96.9% in the group vaccinated with 1/25 dose [titre 4.7 $\log_2$] / 81.3% in group vaccinated with 1/50 dose [titre 3.6 $\log_2$], 50 % in group receiving 1/100 dose [titre 2.6 $\log_2$] and 0% in control group [titre 0 $\log_2$]
Conclusion	the smallest dose of the vaccine correspond to not less than 50 PD_{50} ; which is compliant with the requirements of the European Pharmacopoeia relevant monograph (0870).

Study aim	Onset of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml)
Animals and application scheme (study groups)	Commercial layer type chickens 14 weeks old not previously vaccinated Vaccinates: 40 layers receiving 1 vaccine dose Controls: 12 SPF chickens
Challenge	21 days after vaccination, challenge of 22 vaccinates and 12 controls with virulent strain Herts 33/56 of NDV
Follow up / evaluation criteria*	During 21 days investigation of ND specific signs and serological testing on day 21 (inhibition of hemagglutination)
Results	All control birds died within 5 days after challenge infection – 100 % of the vaccinated were protected – seroconversion after vaccination
Conclusion	The vaccine protects chickens against Newcastle disease (mortality) 21 days after vaccination

Study aim	Duration of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml)
Animals and application scheme (study groups)	Commercial layer type chickens 14 weeks old not previously vaccinated Vaccinates: 83 layers receiving 1 vaccine dose Controls: 12 SPF chickens
Challenge	46 weeks after vaccination (60 weeks old), challenge of 22 vaccinates and 12 controls with virulent strain Herts 33/56 of NDV
Follow up /	During 21 days investigation of ND specific signs and serological testing

evaluation criteria*	(inhibition of hemagglutination) – detection of virus shedding in cloacal and oropharyngeal swabs 3, 5 and 7 days after challenge
Results	All control birds died within 4 days after challenge infection – 100 % of the vaccinated were protected – shedding of the virus was significantly reduced – seroconversion after vaccination
Conclusion	The vaccine protects chickens against Newcastle disease (mortality) till 60 weeks of age

Efficacy of the IB M-41 component

Study aim	immunogenicity
vaccine	CEVAC MEGAMUNE K administered by IM route CEVAC Mass L and CEVAC IBird given by spray
Animals and application scheme (study groups)	group: Vaccination scheme GA – 20 SPF chicks: Controls GB – 20 SPF chicks: CEVAC MEGAMUNE 17 weeks of age GC – 20 SPF chicks: Live priming 2 days of age + CEVAC MEGAMUNE 17 weeks of age GD – 20 SPF chicks: Live priming 2 days of age
Challenge	11 weeks after vaccination (28 weeks of age) challenge with virulent IBV serotype Massachusetts via oculonasal route
Follow up / evaluation criteria*	Assessment of respiratory clinical signs during 5 days – scoring of tracheal rales – after euthanasia of 10 birds of each group, ciliary activity & calculation of mean ciliostasis score Serology at 27, 29 & 30 weeks of age
Results	parameter / GA / GB / GC / GD Clinical scores: 2.3[c] / 0.1[d] / 0.1[a] / 1.6[b] Ciliary score: 39[c] / 29.3[d] / 8.5[a] / 20.7[b] [a/b] : significantly better in group C compared to group D [c/d] : significantly better in group B compared to group A serological titres of chickens from group C significantly higher than those of group D – evidence of a booster effect
Conclusion	The vaccine and vaccine strain comply with the relevant monograph (0959) and requirement of the European Pharmacopoeia for respiratory signs.

Study aim	immunogenicity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC Mass L & CEVAC IBird given by spray
Animals and application scheme (study groups)	<table><tr><td>group</td><td>Vaccination scheme</td></tr><tr><td>GA – 50 SPF chicks</td><td>Controls</td></tr><tr><td>GB – 50 SPF chicks</td><td>CEVAC MEGAMUNE 17 weeks of age</td></tr><tr><td>GC – 50 SPF chicks</td><td>Live priming 2 days of age + CEVAC MEGAMUNE 17 weeks of age</td></tr><tr><td>GD – 49 SPF chicks</td><td>Live priming 2 days of age</td></tr></table>
Challenge	11 weeks after vaccination (28 weeks of age) challenge with virulent IBV serotype Massachusetts via oculonasal route
Follow up / evaluation criteria*	Individual egg collection - assessment of quantity & quality of eggs during 5 weeks 2 and 3 days after challenge scoring of tracheal rales serology
Results	<table><tr><td>parameter</td><td>GA</td><td>GB</td><td>GC</td><td>GD</td></tr><tr><td>Nb of egg/bird/day after challenge</td><td>0.68</td><td>0.93</td><td>0.86</td><td>0.79</td></tr><tr><td>Nb of good quality eggs/bird/day</td><td>0.67</td><td>0.91</td><td>0.86</td><td>0.76</td></tr><tr><td>Tracheal rale 2nd day</td><td>1</td><td>0.3</td><td>0.3</td><td>1.5</td></tr><tr><td>Tracheal rale 3rd day</td><td>1.5</td><td>0.3</td><td>0.1</td><td>1.5</td></tr></table> Significant greater results were observed in birds receiving CEVAC MEGAMUNE.
Conclusion	The vaccine and vaccine strain comply with the relevant monograph (0959) and requirement of the European Pharmacopoeia for egg drop.

Study aim	Onset of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC Mass L & CEVAC IBird given by spray
Animals and application scheme (study groups)	Commercial layer chickens <table><tr><td>group</td><td>Vaccination scheme</td></tr><tr><td>G1 – 80 commercial layers</td><td>Live priming (CEVAC Mass L at day old & 6 weeks of age – CEVAC IBird at 3 & 9 weeks of age) + CEVAC MEGAMUNE 17 weeks of age</td></tr><tr><td>G2 – 80 commercial layers</td><td>Controls</td></tr><tr><td>G3 – 80 commercial layers</td><td>Live priming + CEVAC MEGAMUNE 17 weeks of age</td></tr></table>
Challenge	4 weeks after vaccination (21 weeks of age) challenge of chicks from groups 1 & 2 with virulent IBV Mass 41 via oculonasal route
Follow up / evaluation criteria*	Monitoring of egg production for 4 weeks (quantity, quality) In 20 birds from G1 and 10 birds from G2, respiratory signs with scoring (2,3

<table>
<tr><td></td><td>& 4 days post challenge), ciliary activity (7 days post challenge) & virus shedding (4 & 7 days post challenge – palatinal swabs)
serology</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>parameter</td><td>G1</td><td>G2</td><td>G3</td></tr>
<tr><td>Nb of egg/bird/day after challenge</td><td>60 birds
0.81*</td><td>70 birds
0.67</td><td>80 birds
0.88</td></tr>
<tr><td>Nb of good quality eggs/bird/day</td><td>60 birds
0.80*</td><td>70 birds
0.64</td><td>80 birds
0.87</td></tr>
<tr><td>Respiratory signs</td><td>0/20</td><td>6/10</td><td>-</td></tr>
<tr><td>Ciliary activity</td><td>20 birds
14.7*</td><td>10 birds
38.6</td><td>-</td></tr>
<tr><td>Virus shedding</td><td>20 birds
3.7*</td><td>10 birds
4.8</td><td>-</td></tr>
</table>
Seroconversion in the group 1
</td></tr>
<tr><td>Conclusion</td><td>Efficacy of the vaccine in primed chickens to reduce effects of IB infection (serotype Massachusetts) on egg drop production, egg quality and to reduce clinical signs, damage of the trachea and shedding of the virus 4 weeks after vaccination is established.</td></tr>
</table>

<table>
<tr><td>Study aim</td><td>Duration of immunity</td></tr>
<tr><td>vaccine</td><td>CEVAC MEGAMUNE K administered by IM route (0.5 ml)
CEVAC Mass L & CEVAC IBird given by spray</td></tr>
<tr><td>Animals and application scheme (study groups)</td><td>Commercial layer chickens
<table>
<tr><td>group</td><td>Vaccination scheme</td></tr>
<tr><td>G1 – 80 commercial layers</td><td>Live priming (CEVAC Mass L at day old & 6 weeks of age – CEVAC IBird at 3 & 9 weeks of age) + CEVAC MEGAMUNE 17 weeks of age</td></tr>
<tr><td>G2 – 80 commercial layers</td><td>Controls</td></tr>
<tr><td>G3 – 80 commercial layers</td><td>Live priming + CEVAC MEGAMUNE 17 weeks of age</td></tr>
</table>
</td></tr>
<tr><td>Challenge</td><td>28 weeks after vaccination (45 weeks of age) challenge of chicks from groups 1 & 2 with virulent IBV serotype Massachusetts via oculonasal route</td></tr>
<tr><td>Follow up / evaluation criteria*</td><td>Monitoring of egg production for 4 weeks (quantity, quality)
In 20 birds from G1 and 10 birds from G2, respiratory signs with scoring (2,3 & 4 days post challenge), ciliary activity (7 days post challenge) & virus shedding (4 & 7 days post challenge – palatinal swabs)
serology</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>parameter</td><td>G1</td><td>G2</td><td>G3</td></tr>
<tr><td>Nb of egg/bird/day after challenge - difference</td><td>69 birds
0.06 (0.20)*</td><td>63 birds
-0.06 (0.21)</td><td>79 birds
-0.01 (0.10)</td></tr>
<tr><td>Nb of good quality</td><td>69 birds</td><td>63 birds</td><td>79 birds</td></tr>
</table>
</td></tr>
</table>

	eggs/bird/day - difference: 0.04 (0.20)* / -0.07 (0.21) / -0.01 (0.11) Respiratory signs: 0/10* / 6/10 / - Ciliary activity: 7.0 (8.2)* / 38.4 (3.3) / - Virus shedding: 4.7 (0.7)* / 7.4 (0.4) / - Difference between pre ad post-challenge has been assessed in each group. In group 1 there is an increase in daily egg production and no drop of good quality egg.
Conclusion	Efficacy of the vaccine in primed chickens to reduce effects of IBDV infection (serotype Massachusetts) on egg drop production, egg quality and to reduce clinical signs, damage of the trachea and shedding of the virus 28 weeks after vaccination is established.

<table>
<tr><td>Study aim</td><td>Duration of immunity</td></tr>
<tr><td>vaccine</td><td>CEVAC MEGAMUNE K administered by IM route (0.5 ml)
CEVAC Mass L & CEVAC IBird given by spray</td></tr>
<tr><td>Animals and application scheme (study groups)</td><td>Commercial layer chickens
<table><tr><td>group</td><td>Vaccination scheme</td></tr><tr><td>G1 – 80 commercial layers</td><td>Live priming (CEVAC Mass L at day old & 6 weeks of age – CEVAC IBird at 3 & 9 weeks of age) + CEVAC MEGAMUNE 17 weeks of age</td></tr><tr><td>G2 – 80 commercial layers</td><td>Controls</td></tr><tr><td>G3 – 80 commercial layers</td><td>Live priming + CEVAC MEGAMUNE 17 weeks of age</td></tr></table></td></tr>
<tr><td>Challenge</td><td>43 weeks after vaccination (60 weeks of age) challenge of chicks from groups 1 & 2 with virulent IBV Mass 41 via oculonasal route</td></tr>
<tr><td>Follow up / evaluation criteria*</td><td>Monitoring of egg production for 4 weeks (quantity, quality)
In 20 birds from G1 and 10 birds from G2, respiratory signs with scoring (2,3 & 4 days post challenge), ciliary activity (7 days post challenge) & virus shedding (4 & 7 days post challenge – palatinal swabs)
serology</td></tr>
<tr><td>Results</td><td><table><tr><td>parameter</td><td>G1</td><td>G2</td><td>G3</td></tr><tr><td>Nb of egg/bird/day after challenge</td><td colspan="3" rowspan="2">No valid results</td></tr><tr><td>Nb of good quality eggs/bird/day</td></tr><tr><td>Respiratory signs</td><td>2/10*</td><td>10/10</td><td>-</td></tr><tr><td>Ciliary activity</td><td>17.6 (10.5)*</td><td>40.0 (0.0)</td><td>-</td></tr><tr><td>Virus shedding</td><td>6.5 (0.5)*</td><td>7.8 (0.2)</td><td>-</td></tr></table></td></tr>
<tr><td>Conclusion</td><td>Efficacy of the vaccine in primed chickens to reduce effects of IBV infection linked to strain Massachussets to reduce clinical signs, damage of the trachea and shedding of the virus 43 weeks after vaccination is established.</td></tr>
</table>

Efficacy of the IB QX component

Study aim	immunogenicity
vaccine	CEVAC MEGAMUNE K administered by IM route CEVAC Mass L and CEVAC IBird given by spray
Animals and application scheme (study groups)	group: Vaccination scheme GA – 10 SPF chicks: Controls GB – 10 SPF chicks: CEVAC MEGAMUNE 17 weeks of age GC – 10 SPF chicks: Live priming 2 days of age + CEVAC MEGAMUNE 17 weeks of age GD – 10 SPF chicks: Live priming 2 days of age
Challenge	23 weeks after vaccination (40 weeks of age) challenge with virulent IBV serotype QX via oculonasal route
Follow up / evaluation criteria*	Assessment of respiratory clinical signs during 5 days – scoring of tracheal rales – after euthanasia of all birds, ciliary activity & calculation of mean ciliostasis score Serology at 34 weeks of age
Results	parameter: GA / GB / GC / GD Scoring tracheal rales 7th day: 0.8[a] / 0.3[b] / 0.2[c] / 1.1[d] Ciliary score: 33[a] / 21.5[b] / 18.4[c] / 20[c] [a/b] : significantly better in group C compared to group D [c/d] : significantly better in group B compared to group A serological titres of chickens from group C significantly higher than those of group D – evidence of a booster effect
Conclusion	The vaccine and vaccine strain comply with the relevant monograph (0959) and requirement of the European Pharmacopoeia for respiratory signs.

Study aim	immunogenicity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC Mass L & CEVAC IBird given by spray
Animals and application scheme (study groups)	group: Vaccination scheme GA – 50 SPF chicks: Controls GB – 48 SPF chicks: CEVAC MEGAMUNE 17 weeks of age GC – 48 SPF chicks: Live priming 2 days of age + CEVAC MEGAMUNE 17 weeks of age GD – 50 SPF chicks: Live priming 2 days of age
Challenge	21 weeks after vaccination (38 weeks of age) challenge with virulent IBV serotype QX via oculonasal route
Follow up /	Individual egg collection - assessment of quantity & quality of eggs during 5

evaluation criteria*	weeks 7 days after challenge scoring of tracheal rales
Results	<table><tr><td>parameter</td><td>GA</td><td>GB</td><td>GC</td><td>GD</td></tr><tr><td>Nb of egg/bird/day after challenge</td><td>0.49[a]</td><td>0.58[b]</td><td>0.77[c]</td><td>0.67[d]</td></tr><tr><td>Nb of good quality eggs/bird/day</td><td>0.49[a]</td><td>0.57[b]</td><td>0.75[c]</td><td>0.67[d]</td></tr><tr><td>Tracheal rale 7th day</td><td>0.9[a]</td><td>0.8[a]</td><td>0.4[c]</td><td>0.6[c]</td></tr></table>
Conclusion	Significant protection against egg drop after challenge is observed in vaccinated groups – in primed chickens significant protection against respiratory signs is also established.

Study aim	Onset of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC Mass L & CEVAC IBird given by spray
Animals and application scheme (study groups)	Commercial layer chickens <table><tr><td>group</td><td>Vaccination scheme</td></tr><tr><td>G1 – 80 commercial layers</td><td>Live priming (CEVAC Mass L at day old & 6 weeks of age – CEVAC IBird at 3 & 9 weeks of age) + CEVAC MEGAMUNE 17 weeks of age</td></tr><tr><td>G2 – 80 commercial layers</td><td>Controls</td></tr><tr><td>G3 – 80 commercial layers</td><td>Live priming + CEVAC MEGAMUNE 17 weeks of age</td></tr></table>
Challenge	29 days after vaccination (21 weeks of age) challenge of chicks from groups 1 & 2 with virulent IBV serotype QX via oculonasal route
Follow up / evaluation criteria*	Monitoring of egg production for 4 weeks (quantity, quality) In 20 birds from G1 and 10 birds from G2, respiratory signs with scoring (2,3 & 4 days post challenge), ciliary activity (7 days post challenge) & virus shedding (3 days post challenge – palatinal swabs) serology
Results	<table><tr><td>parameter</td><td>G1</td><td>G2</td><td>G3</td></tr><tr><td>Nb of egg/bird/day after challenge</td><td>60 birds 0.84 (0.19)*</td><td>70 birds 0.53 (0.24)</td><td>80 birds 0.88 (0.11)</td></tr><tr><td>Nb of good quality eggs/bird/day</td><td>60 birds 0.83 (0.20)*</td><td>70 birds 0.52 (0.24)</td><td>80 birds 0.87 (0.12)</td></tr><tr><td>Respiratory signs</td><td>1/20*</td><td>6/10</td><td></td></tr><tr><td>Ciliary activity</td><td>20 birds 22.7(14.9)*</td><td>10 birds 39.9 (0.3)</td><td></td></tr><tr><td>Virus shedding</td><td>20 birds 3.5 (1.0)*</td><td>10 birds 5.1 (0.3)</td><td></td></tr></table>

Conclusion	Efficacy of the vaccine in primed chickens to reduce effects of IBDV infection linked to serotype QX on egg drop production, egg quality and to reduce clinical signs, damage of the trachea and shedding of the virus 4 weeks after vaccination is established.

Study aim	Duration of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC Mass L & CEVAC IBird given by spray
Animals and application scheme (study groups)	Commercial layer chickens group: Vaccination scheme G1 – 80 commercial layers: Live priming (CEVAC Mass L at day old & 6 weeks of age – CEVAC IBird at 3 & 9 weeks of age) + CEVAC MEGAMUNE 17 weeks of age G2 – 80 commercial layers: Controls G3 – 80 commercial layers: Live priming + CEVAC MEGAMUNE 17 weeks of age
Challenge	28 weeks after vaccination (45 weeks of age) challenge of chicks from groups 1 (80) & 2 (75) with virulent IBV serotype QX via oculonasal route
Follow up / evaluation criteria*	Monitoring of egg production for 4 weeks (quantity, quality) In 10 birds from G1 and G2, respiratory signs with scoring (2, 3 & 4 days post challenge), ciliary activity (7 days post challenge) & virus shedding (4 & 7 days post challenge – palatinal swabs)
Results	

parameter	G1	G2	G3
Nb of egg/bird/day after challenge - difference	69 chickens 0.05 (0.19)	64 chickens -0.19 (0.28)	79 chickens 0.0 (0.10)
Nb of good quality eggs/bird/day - difference	69 chickens 0.05 (0.20)	64 chickens -0.19 (0.28)	79 chickens 0.0 (0.11)
Respiratory signs	40%	80%	
Ciliary activity	20.4 (15.3)*	40.0 (0.0)	
Virus shedding	5.9 (0.8)*	7.7 (0.5)	-

Difference between pre and post-challenge has been assessed in each group. In group 1 there is an increase in daily egg production and no drop of good quality egg.

Conclusion	Efficacy of the vaccine in primed chickens to reduce effects of IBV infection (serotype QX) on egg drop production, egg quality and to reduce clinical signs, damage of the trachea and shedding of the virus 28 weeks after vaccination is established.

<table>
<tr><td>Study aim</td><td>Duration of immunity</td></tr>
<tr><td>vaccine</td><td>CEVAC MEGAMUNE K administered by IM route (0.5 ml)
CEVAC Mass L & CEVAC IBird given by spray</td></tr>
<tr><td>Animals and application scheme (study groups)</td><td>Commercial layer chickens
<table><tr><td>group</td><td>Vaccination scheme</td></tr><tr><td>G1 – 80 commercial layers</td><td>Live priming (CEVAC Mass L at day old & 6 weeks of age – CEVAC IBird at 3 & 9 weeks of age) + CEVAC MEGAMUNE 17 weeks of age</td></tr><tr><td>G2 – 80 commercial layers</td><td>Controls</td></tr><tr><td>G3 – 80 commercial layers</td><td>Live priming + CEVAC MEGAMUNE 17 weeks of age</td></tr></table></td></tr>
<tr><td>Challenge</td><td>43 weeks after vaccination (60 weeks of age) challenge of chicks from groups 1 & 2 with virulent IBV serotype QX via oculonasal route</td></tr>
<tr><td>Follow up / evaluation criteria*</td><td>Monitoring of egg production for 4 weeks (quantity, quality)
In 10 birds from G1 and 10 birds from G2, respiratory signs with scoring (2,3 & 4 days post challenge), ciliary activity (7 days post challenge) & virus shedding (4 & 7 days post challenge – palatinal swabs)</td></tr>
<tr><td>Results</td><td><table><tr><td>parameter</td><td>G1</td><td>G2</td><td>G3</td></tr><tr><td>Nb of egg/bird/day after challenge – difference</td><td>69 chicks
0.02 (0.35)*</td><td>62 chicks
-0.17 (0.31)</td><td>78 chicks
0.0 (0.09)</td></tr><tr><td>Nb of good quality eggs/bird/day – difference</td><td>69 chicks
0.05 (0.35)*</td><td>62 chicks
-0.14 (0.32)</td><td>78 chicks
0.0 (0.10)</td></tr><tr><td>Respiratory signs</td><td>3/10</td><td>7/10</td><td></td></tr><tr><td>Ciliary activity</td><td>22.9 (13.2)*</td><td>40.0 (0.0)</td><td></td></tr><tr><td>Virus shedding</td><td>6.3 (0.7)*</td><td>7.4 (0.4)</td><td></td></tr></table></td></tr>
<tr><td>Conclusion</td><td>Efficacy of the vaccine in primed chickens to reduce effects of IBV (serotype QX) infection on egg drop production, egg quality and to reduce damage of the trachea and shedding of the virus 43 weeks after vaccination is established.</td></tr>
</table>

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Efficacy of the EDS component

<table>
<tr><td>Study aim</td><td>immunogenicity</td></tr>
<tr><td>vaccine</td><td>CEVAC MEGAMUNE K administered by IM route (0.5 ml)</td></tr>
<tr><td>Animals and application scheme (study groups)</td><td>Vaccination at 14 weeks of age with 1 dose (0.5 ml)

<table><tr><td>group</td><td>Vaccination scheme</td></tr><tr><td>G6 – 70 SPF chicks</td><td>CEVAC MEGAMUNE vaccinated challenged</td></tr><tr><td>G7 – 70 SPF chicks</td><td>Non-vaccinated challenged</td></tr><tr><td>G8 – 70 SPF chicks</td><td>CEVAC MEGAMUNE</td></tr><tr><td>G9 – 70 SPF chicks</td><td>CEVAC MEGAMUNE vaccinated challenged</td></tr><tr><td>G10 – 70 SPF chicks</td><td>Non-vaccinated challenged</td></tr></table></td></tr>
<tr><td>Challenge</td><td>On D112 (30 weeks of age) challenge of groups 6 & 7
On D300 (57 weeks of age) challenge of groups 9 & 10 with virulent EDS virus</td></tr>
<tr><td>Follow up / evaluation criteria*</td><td>Daily investigation of egg production and egg shell quality during 4 weeks after each challenge</td></tr>
<tr><td>Results</td><td>Seroconversion of vaccinated groups

<table><tr><td></td><td>Average nb eggs/bird/day after challenge D113-D140</td><td>Average nb good quality eggs/bird/day after challenge D113-D140</td></tr><tr><td>G6
Vaccinated – challenged</td><td>0.86</td><td>0.77</td></tr><tr><td>G7
Not vaccinated - challenged</td><td>0.67*</td><td>0.55*</td></tr><tr><td>G8
Vaccinated – not challenged</td><td>0.84</td><td>0.83</td></tr><tr><td></td><td>Average nb eggs/bird/day after challenge D301-D328</td><td>Average nb good quality eggs/bird/day after challenge D301-D328</td></tr><tr><td>G9
Vaccinated – challenged</td><td>0.76</td><td>0.69</td></tr><tr><td>G10
Not vaccinated - challenged</td><td>0.58*</td><td>0.46*</td></tr><tr><td>G8
Vaccinated – not challenged</td><td>0.76</td><td>0.75</td></tr></table></td></tr>
<tr><td>Conclusion</td><td>Immunogenicity of the EDS component is established in conformity with relevant Ph. Eur. monograph requirements (1202)</td></tr>
</table>

Study aim	Onset of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml)
Animals and application scheme (study groups)	Commercial layer chickens 17 weeks of age group: Vaccination scheme G1 – 70 layers: CEVAC MEGAMUNE challenged G2 – 70 layers: Non-vaccinated challenged G3 – 70 layers: CEVAC MEGAMUNE
Challenge	On day 28 (4 weeks after vaccination) challenge of groups G1 & G2 with virulent EDS virus (per os)
Follow up / evaluation criteria*	Daily investigation of egg production (quantity and quality during 4 weeks Serology (D0 and prior to challenge)
Results	Seroconversion of the vaccinated chickens Average nb eggs/hen/day D29-D56 / Average nb good quality eggs/hen/day D29-D56 G1 – 70 – vaccinated: 0.82 (0.12) / 0.78 (0.14) G2 – 70 - controls: 0.69 (0.12)* / 0.55 (0.15)* G3 – 70 – non challenged: 0.84 (0.14) / 0.84 (0.13)
Conclusion	Onset of immunity is determined at 4 weeks after vaccination

Study aim	Duration of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml)
Animals and application scheme (study groups)	Commercial layer chickens 17 weeks of age group: Vaccination scheme G1 – 68 layers: CEVAC MEGAMUNE challenged G2 – 41 layers: Non-vaccinated challenged G3 – 70 layers: CEVAC MEGAMUNE G4 – 70 layers: CEVAC MEGAMUNE challenged G5 – 70 layers: Non-vaccinated challenged
Challenge	On day 301 (60 weeks of age) challenge of groups 4 & 5 and on day 479 challenge of group 1 (85 weeks of age) and group 2 (61 weeks of age) with virulent EDS virus (per os)
Follow up / evaluation criteria*	Daily investigation of egg production (quantity and quality during 4 weeks) Serology (D0 and prior to challenge)

Results	Seroconversion of the vaccinated chickens
Conclusion	Duration of immunity is determined at 68 weeks after vaccination

	Average nb eggs/bird/day after challenge D302-D329	Change in daily production after challenge egg/hen/day D294-D301 vs D302-D329	Average nb good quality eggs/bird/day after challenge D302-D329	Change average nb good quality eggs after challenge egg/hen/day D294-D301 vs D302-D329
G3 – 68 chickens V – not C	0.89 (0.11)	-0.01 (0.12)	0.89 (0.11)	-0.01 (0.12)
G4 – 69 chickens V - C	0.80 (0.14)	0.01 (0.17)	0.75 (0.15)	0.01 (0.19)
G5 – 70 chickens Not V - C	0.61 (0.14)	-0.24 (0.18)	0.48 (0.15)	-0.32 (0.20)
	Average nb eggs/bird/day after challenge	Change in daily production after challenge egg/hen/day D466-D479 vs D480-D507	Average nb good quality eggs/bird/day after challenge	Change in daily production after challenge egg/hen/day D466-D479 vs D480-D507
G1 – 66 chickens V – C		0.01 (0.21)		0.03 (0.24)
G2 – 41 chickens Not V – C		-0.20 (0.25)		-0.30* (0.28)

Efficacy of the TRT component

Study aim	Onset of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC META L
Animals and application scheme (study groups)	<table><tr><th>group</th><th>Vaccination scheme</th></tr><tr><td>G1 – 50 commercial layers</td><td>CEVAC META L (spray / 2 weeks of age) and MEGAMUNE (IM / 14 weeks of age)</td></tr><tr><td>G2 – 50 commercial layers</td><td>-</td></tr><tr><td>G3 – 10 SPF chickens</td><td>-</td></tr></table>
Challenge	On day 25 (4 weeks after vaccination) challenge of groups G1 & G2 (30 chicks) and G3 (10 chicks) with virulent avian pneumovirus (oculonasal route)
Follow up / evaluation criteria*	Observation for 10 days – recording of clinical signs and scoring – virus shedding on D28 & D30 (oro-palatinal swab samples) - serology
Results	Higher serological titres in the vaccinated chickens <table><tr><td></td><td colspan="6">Mean scores for respiratory clinical signs after challenge D28-D35</td></tr><tr><td></td><td>D28</td><td>D29</td><td>D30</td><td>D31</td><td>D32</td><td>D35</td></tr><tr><td>G1</td><td>0.0</td><td>0.0</td><td>0.1</td><td>0.0</td><td>0.2</td><td>0.2</td></tr><tr><td>G2</td><td>0.0</td><td>0.2</td><td>1.5*</td><td>1.9*</td><td>1.6*</td><td>0.4</td></tr><tr><td>G3</td><td>1.3*</td><td>2.1*</td><td>2.9*</td><td>2.7*</td><td>1.8*</td><td>1.1*</td></tr></table> <table><tr><td></td><td colspan="2">Shedding of challenge virus log_{10} REU</td></tr><tr><td></td><td>D28</td><td>D30</td></tr><tr><td>G1</td><td>0.9*</td><td>0.3*</td></tr><tr><td>G2</td><td>4.5</td><td>3.4</td></tr><tr><td>G3</td><td>4.5</td><td>2.7</td></tr></table>
Conclusion	Onset of immunity is determined at –4 weeks after vaccination in chickens previously primed with live TRT vaccine before vaccination with CEVAC MEGAMUNE

Study aim	Duration of immunity
vaccine	CEVAC MEGAMUNE K administered by IM route (0.5 ml) CEVAC META L
Animals and application scheme (study groups)	Commercial layer chickens 14 weeks of age <table><tr><th>group</th><th>Vaccination scheme</th></tr><tr><td>G1 - 50 commercial layers</td><td>CEVAC META L (spray / 2 weeks of age) and MEGAMUNE (IM / 14 weeks of age)</td></tr><tr><td>G2 – 50 commercial layers</td><td>-</td></tr><tr><td>G3 – 10 SPF chickens</td><td>-</td></tr></table>
Challenge	46 weeks after vaccination (60 weeks of age) challenge with virulent avian pneumovirus of 30/20 chickens from G1 & G2 and 10 from G3

<table>
<tr><td>Follow up / evaluation criteria*</td><td>Observation for 10 days after challenge
Virus shedding (oro-palatinal swabs)
serology</td></tr>
<tr><td>Results</td><td>higher serological titre in vaccinated chickens – SPF controls remain seronegative

<table>
<tr><td></td><td colspan="6">Mean scores for respiratory clinical signs after challenge D322-D329</td></tr>
<tr><td></td><td>D322</td><td>D323</td><td>D324</td><td>D325</td><td>D326</td><td>D329</td></tr>
<tr><td>G1</td><td>0.2</td><td>0.1</td><td>0.0</td><td>0.1</td><td>0.0</td><td>0.0</td></tr>
<tr><td>G2</td><td>0.6</td><td>2.0*</td><td>2.0*</td><td>0.6*</td><td>0.1</td><td>0.1</td></tr>
<tr><td>G3</td><td>2.0</td><td>2.6</td><td>2.9</td><td>2.2</td><td>1.6</td><td>0.4</td></tr>
</table>

<table>
<tr><td></td><td colspan="2">Shedding of challenge virus log_{10} REU</td></tr>
<tr><td></td><td>D322</td><td>D324</td></tr>
<tr><td>G1</td><td>0.5*</td><td>0.0*</td></tr>
<tr><td>G2</td><td>4.7</td><td>1.3</td></tr>
<tr><td>G3</td><td>3.9</td><td>0.6</td></tr>
</table>
</td></tr>
<tr><td>Conclusion</td><td>Duration of immunity is determined at 46 weeks after vaccination in chickens previously primed with live TRT vaccine before vaccination with CEVAC MEGAMUNE</td></tr>
</table>

4.C. Clinical trials

Efficacy of vaccination was also demonstrated under field conditions in 2 controlled field trial(s) in Hungary.

The first one included 75200 commercial layers receiving live priming with authorised vaccine against Newcastle disease, infectious bronchitis and avian pneumovirus before vaccination with CEVAC MEGAMUNE at 17 weeks of age (37600 layers) or one comparator vaccine. No adverse reactions related to vaccination were observed.

36 days after vaccination 3 groups of 20 layers were taken to laboratory and respectively challenged with virulent avian metapneumovirus, virulent IBV serotype QX and virulent IBV serotype Massachusetts. Groups of 10 SPF chickens were included and challenged as controls.

Significant reduction of respiratory signs and shedding of challenged virus in vaccinated chickens was observed after infection with avian pneumovirus; significant reduction of detrimental effect on ciliary activity and shedding of challenged virus in vaccinates was also established after experimental infection with infectious bronchitis virus serotypes Massachusetts or QX.

The 2nd study involved 57460 commercial layers receiving live priming with authorised vaccines against Newcastle disease, infectious bronchitis and avian pneumovirus before vaccination with CEVAC MEGAMUNE at 17 weeks of age (23930 layers) or one comparator vaccine. No adverse reactions related to vaccination were observed during 41 weeks of observation. Average serological titres induced after vaccination with CEVAC MEGAMUNE were similar to these observed after vaccination with comparator vaccine.

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 are acceptable.

MODULE 4

POST-AUTHORISATION PROCEDURES

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/labelling/package leaflet is/are available in the Union Product Database (UPD).

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

Sequence of significant variations

Summary of change (Application number)	Approval date