BIOVETA, a.s., Komenského 212, 683 23 Ivanovice na Hané, CZECH REPUBLIC
Phone: 00420-517318609 Fax: 00420-517363319

CERTIFICATE OF ANALYSIS

Product: **Biocan R vakcina A.U.V.**

Batch No.: **01 56 23 A** 10 doses
Expiry: 29.06.2018
Date of production: 30.06.2016

Results of analysis:

Tests	**Specification**	**Results**
Appearance	Slightly pink solution, which might content fine sediment.	conforms
Content of the original package	min. 1 ml, 5 ml, 10 ml, 20 ml or 100 ml	10.5 ml
Sterility	Vaccine should be sterile.	sterile
Potency	The vaccine must contain min. 2 IU/ml.	6.46 IU/ml
Identity	In the serum of vaccinated animals must be specific antibody levels ≥ 0.5 IU/ml.	1.69 IU/ml
Inactivation	The vaccine must not contain a vivid rabies virus.	conforms
pH	7.2 – 8.2	7.65
Aluminium oxide	0.15 – 0.30 %	0.15995 %
Merthiolate	0.0085 – 0.0115 %	0.0106 %
Air tightness	No colour change.	conforms

I certify that this product has been tested in the laboratories of Bioveta a.s. and has been found to meet specification requirements. Preparation is suitable with control regulations of the valid PN No. 233, spec.03.

Bioveta, a.s. Czech Republic

.....30/09/2016
Mgr. Hana Nezvalová
HEAD of QC, QP

BIOVETA, a.s., Komenského 212, 683 23 Ivanovice na Hané, CZECH REPUBLIC
Phone: 00420-517318609 Fax: 00420-517363319

CERTIFICATE OF ANALYSIS

Product: **Biocan R vakcina A.U.V.**

Batch No.: **01 56 23 B** 10 doses
Expiry: 29.06.2018
Date of production: 30.06.2016

Results of analysis:

Tests	**Specification**	**Results**
Appearance	Slightly pink solution, which might content fine sediment.	conforms
Content of the original package	min. 1 ml, 5 ml, 10 ml, 20 ml or 100 ml	10.6 ml
Sterility	Vaccine should be sterile.	sterile
Potency	The vaccine must contain min. 2 IU/ml.	6.46 IU/ml
Identity	In the serum of vaccinated animals must be specific antibody levels ≥ 0.5 IU/ml.	1.69 IU/ml
Inactivation	The vaccine must not contain a vivid rabies virus.	conforms
pH	7.2 – 8.2	7.62
Aluminium oxide	0.15 – 0.30 %	0.15995 %
Merthiolate	0.0085 – 0.0115 %	0.0106 %
Air tightness	No colour change.	conforms

I certify that this product has been tested in the laboratories of Bioveta a.s. and has been found to meet specification requirements. Preparation is suitable with control regulations of the valid PN No. 233, spec.03.

Bioveta, a.s. Ivanovice na Hané Komenského 212/12 Czech Republic

.....29/09/2016
Mgr. Hana Nezvalová
HEAD of QC, QP

ÚSTAV PRO STÁTNÍ KONTROLU VETERINÁRNÍCH BIOPREPARÁTŮ A LÉČIV
INSTITUTE FOR STATE CONTROL OF VETERINARY BIOLOGICALS AND MEDICINES
Hudcova 56a, 621 00 Brno-Medlánky, Czech Republic
Tel.: +420-541 518 211 Fax.: +420-541 210 026 E-mail: uskvbl@uskvbl.cz

EUROPEAN COMMUNITY/EEA OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Certifikát Evropského společenství /EEA o úředním uvolnění šarže pro imunologické veterinární léčivé přípravky

Institute for State Control of Veterinary Biologicals and Medicines examined the batch of immunological veterinary medicinal product specified bellow under the Article 82 of Directive 2001/82/EC as amended by Directive 2004/28/EC and in accordance with the current Procedure for Official Control Authority Batch Release of immunological veterinary medicinal products in the European Community:
Ústav pro státní kontrolu veterinárních biopreparátů a léčiv prověřil níže specifikovaný imunologický veterinární léčivý přípravek podle článku 82 Směrnice 2001/82/ES ve znění Směrnice 2004/28/ES a v souladu s aktuálním pokynem Postup pro úřední uvolňování šarží imunologických veterinárních léčivých přípravků kontrolním úřadem v Evropském společenství:

Trade name: *Obchodní název:*	**BIOCAN R injekční suspenze**
International non-proprietary Name/Ph.Eur. name/common name: *Mezinárodní nechráněný název / název uvedený v Ph. Eur. / běžný název*	**Vaccina ad usum veterinarium** **Vaccinum rabiei inactivatum ad usum veterinarium**
Name and address of marketing authorisation holder *Název a adresa držitele rozhodnutí o registraci*	**Bioveta a.s.** **Komenského 212** **683 23 Ivanovice na Hané, Czech Republic**
Name and address of manufacturer, if different *Název a adresa výrobce, pokud jsou odlišné*	--
Marketing authorisation number (Member State/EC) issued by *Číslo rozhodnutí o registraci (členský stát /ES) vydané*	**97/086/02-C**
Manufacturer's batch number(s) appearing on package and other identification numbers associated with this batch (final bulk lot No., final lot No., packaging lot No.) *Číslo výrobní šarže uvedené na obalu a další identifikační čísla vztahující se k této šarži (šarže bulku, finální šarže, šarže balení)*	final bulk lot No. **015623** final lot No. **015623A,B** packaging lot No. **015623A,B**
Batch number of authorised diluent:[1] *Číslo šarže registrovaného zřeďovače:*[1] *(tam, kde je to vhodné)*	--
Type of container: *Druh obalu:*	**10 ml glass bottles with rubber stopper**
Total number of containers in this batch:[2] *Celkový počet obalů v této šarži:*[2]	**18 017 × 10 ml (A)** **5 252 × 10 ml (B)**
Number of doses/volume per container: *Počet dávek/objem obalu:*	**10 ml/10 dose**
Date of start of period of validity: */Datum zahájení doby platnosti:* **Expiry date**/*Datum expirace:*	**30.06.2016 (Blending)** **29.06.2018**

[1] Provision of different batch numbers of authorised diluent to different Member State should not impair mutual recognition of OCABR for the batch of active component covered by certificate, however if a diluent batch different from that on certificate is provided, protocol documentation on the new diluent batch may be requested in addition to the certificate.
Dodávání různých šarží registrovaného zřeďovače do různých členských států by nemělo negativně ovlivnit vzájemné uznání OCABR pro šarži účinné složky jištěné certifikátem, nicméně, pokud je šarže zřeďovače odlišná od šarže uvedené na certifikátu, může být k doplnění certifikátu vyžádána výrobní dokumentace k nové šarži zřeďovače.

[2] If different fillings exist, please indicate
uvede se, pokud jsou plněny rozdílné objemy

Signed/*Podpis*:
Date/*Datum*: 07.09.2016

1. MEMBER STATE SPECIFIC INFORMATION

Identification number for batch to be placed on the market in the Member State (if packaging number different from final number in section 2):	**01 56 23 A, B**
Marketing authorisation number issued by (Member State/EU)	**97/086/02-C**
Target species:	Dogs, cats, catlle, pigs, sheep, goat, horses and ferrets
Total number of containers in this batch (pcs):	18 017 pcs (A) 5 252 pcs (B)
Number of containers the release is applied for:	18 017 pcs (A) 5 252 pcs (B)
Number of doses per container:	10 doses
Number of samples for the competent authority:	10 x 10 ml (A) 1 x 10 ml (B)
Date of expiry:	29.06.2018
Name and address of Marketing Authorisation holder (if different from manufacturer in section 2)	/

2. SUMMARY INFORMATION ON THE FINAL BATCH OF FINISHED PRODUCT

Trade name:	**Biocan R** suspension for injection
Ph.Eur.	Vaccina ad usum veterinarium
Nature of product:	Vaccine against rabies, inactivated
Batch number(s) of finished product:	**01 56 23 A,B**
Pharmaceutical form of final product:	Injection
Type of final container:	10 ml glass bottles with rubber stopper
Date of start of period of validity	30.6.2016(Blending)
Shelf life:	24 months
Storage temperature:	Store in a dark and dry place at the temperature between 2 °C and 8 °C. The vaccine shall not be allowed to freeze.
Name and address of manufacturer:	Bioveta, a.s. Komenského 212/12 683 23 Ivanovice na Hané, Czech Republic
Name and address of the batch control site (if different from that of manufacturer)	/

3. PRODUCTION INFORMATION

Summary information scheme on batch specific production data including dates of different production stages, production sites and identification numbers.

Product name		**Product batch number**	
Biocan R suspension for injection		01 56 23 A,B	
Component.	**Batch / ID No.**	**Site(s) of manufacture**	**Date of manufacture**
Inactivated rabies virus, strain Vnukovo-32	63/2016/RVV	Bioveta, a.s.	17.5.2016
Inactivated rabies virus, strain Vnukovo-32	64/2016/RVV	Bioveta, a.s.	17.5.2016
Inactivated rabies virus, strain Vnukovo-32	66 /2016/RVV	Bioveta, a.s.	24.5.2016
Inactivated rabies virus, strain Vnukovo-32	67/2016/RVV	Bioveta, a.s.	24.5.2016
aluminium hydroxide gel	5227	Brenntag biosector	-
Thiomersal	000 667	Gihon	-

3.1 STARTING MATERIALS

3.1.1 Virus seed lots

Master seed material	**Batch number**
MSV Bio – 16: Sad Vnukovo – 32	109th passage, 29.11.1992
	Date of last testing
	8.7.2010

Working seed material	**Batch number**
WSV Bio – 16: Sad Vnukovo – 32	110th passage, 26.2.2013
	Date of last testing
	30.10.2013

3.1.2 Cell seed lots

Master seed material	**Batch number**
MCS Bio – 101: BHK-21 C13,	139th passage, 27.2.1991
	Date of last testing
	14.5.2010

Working seed material	**Batch number**
WCS Bio – 101: BHK-21 C13,	142nd passage, 27.6.2012
	Date of last testing
	17.6.2013

3.1.3 Other materials of animal origin

Material	**Batch number**
Foetal bovine serum	63/2016/RVV: A10312 – 2859 64/2016/RVV: A10312 – 2859 66/2016/RVV: A10312 – 2859 67/2016/RVV: A10312 – 2859
Calf serum	63/2016/RVV: B30713 – 1840 64/2016/RVV: B30713 – 1840 66/2016/RVV: B30713 – 1840 67/2016/RVV: B30713 – 1840
Trypsin	63/2016/RVV: 555223 64/2016/RVV: 555223 66/2016/RVV: 545223 67/2016/RVV: 555223

3.2 INTERMEDIATE STAGES OF PRODUCTION

3.2.1 Rabies virus, strain Vnukovo-32, batch – 63/2016/RVV

Production step	Start	End	Material	Volume	Other relevant data
Cell passaging	29.4.2015	9.5.2016	trypsin solution culture medium	8.9 l 47.7 l	-
Infection	9.5.2016	9.5.2016	WSV Bio – 16: Sad Vnukovo – 32, 110th passage of 26.2.2013 trypsin solution culture medium	0.08 ml 15 l 75 l	-
Passaging of infected cells	11.5.2016	11.5.2016	trypsin solution culture medium	38 l 193 l	-
Exchange of the cultivation medium	13.5.2016	13.5.2016	maintaining medium	180 l	-
Harvest	17.5.2016	17.5.2016	-	180 l	-
Inactivation	17.5.2016	18.5.2016	Betapropiolactone	90 ml	-
Storage(<-25°C)	18.5.2016	24.6.2016	-	180 l	at temperature at ≤-20°C (max. 6 months)
Storage (2-8°C)	24.6.2016	28.6.2016	-	180 l	at temperature 2-8 °C (max. 1 month)
Concentration (ultrafiltration)	28.6.2016	28.6.2016	-	180 l ----> 57 l	-
Storage (2-8°C)	28.6.2016	30.6.2016	-	-	at temperature 2-8 °C (max. 5 months) or at ≤ -20°C (max. 5 months)

3.2.2. Rabies virus, strain Vnukovo-32, batch 64/2016/RVV

Production step	Start	End	Material	Volume	Other relevant data
Cell passaging	29.4.2016	9.5.2016	trypsin solution culture medium	8.8 l 47.7 l	-
Infection	9.5.2016	9.5.2016	WSV Bio – 16: Sad Vnukovo – 32, 110th passage of 26.2.2013 trypsin solution culture medium	0.08 ml 15 l 75 l	-
Passaging of infected cells	11.5.2016	11.5.2016	trypsin solution culture medium	38 l 193 l	-
Exchange of the cultivation medium	13.5.2016	13.5.2016	maintaining medium	180 l	-
Harvest	17.5.2016	17.5.2016	-	180 l	-
Inactivation	17.5.2016	18.5.2016	Betapropiolactone	90 ml	-
Storage(<-25°C)	18.5.2016	24.6.2016	-	180 l	at temperature at ≤-20°C (max. 6 months)
Storage (2-8°C)	24.6.2016	28.6.2016	-	180 l	at temperature 2-8 °C (max. 1 month)
Concentration (ultrafiltration)	28.6.2016	28.6.2016	-	180 l ----> 56 l	-
Storage (2-8°C)	28.6.2016	30.6.2016	-	-	at temperature 2-8 °C (max. 5 months) or at ≤ -20°C (max. 5 months)

3.2.3. Rabies virus, strain Vnukovo-32, batch 66/2016/RVV

Production step	Start	End	Material	Volume	Other relevant data
Cell passaging	6.5.2016	16.5.2016	trypsin solution culture medium	8.8 l 47.7 l	-
Infection	16.5.2016	16.5.2016	WSV Bio – 16: Sad Vnukovo – 32, 110th passage of 26.2.2013 trypsin solution culture medium	0.08 ml 15 l 75 l	-
Passaging of infected cells	18.5.2016	18.5.2016	trypsin solution culture medium	38 l 193 l	-
Exchange of the cultivation medium	20.5.2016	20.5.2016	maintaining medium	180 l	-
Harvest	24.5.2016	24.5.2016	-	180 l	-
Inactivation	24.5.2016	25.5.2016	Betapropiolactone	90 ml	-
Storage(<-25°C)	25.5.2016	24.6.2016	-	180 l	at temperature at ≤-20°C (max. 6 months)
Storage (2-8°C)	24.6.2016	28.6.2016	-	180 l	at temperature 2-8 °C (max. 1 month)
Concentration (ultrafiltration)	28.6.2016	28.6.2016	-	180 l ----> 56 l	-
Storage (2-8°C)	28.6.2016	30.6.2016	-	-	at temperature 2-8 °C (max. 5 months) or at ≤ -20°C (max. 5 months)

3.2.4. Rabies virus, strain Vnukovo-32, batch 67/2016/RVV

Production step	Start	End	Material	Volume	Other relevant data
Cell passaging	6.5.2016	16.5.2016	trypsin solution culture medium	8.8 l 47.7 l	-
Infection	16.5.2016	16.5.2016	WSV Bio – 16: Sad Vnukovo – 32, 110th passage of 26.2.2013 trypsin solution culture medium	0.08 ml 15 l 75 l	-
Passaging of infected cells	18.5.2016	18.5.2016	trypsin solution culture medium	38 l 193 l	-
Exchange of the cultivation medium	20.5.2016	20.5.2016	maintaining medium	180 l	-
Harvest	24.5.2016	24.5.2016	-	180 l	-
Inactivation	24.5.2016	25.5.2016	Betapropiolactone	90 ml	-
Storage(<-25°C)	25.5.2016	24.6.2016	-	180 l	at temperature at ≤-20°C (max. 6 months)
Storage (2-8°C)	24.6.2016	29.6.2016	-	180 l	at temperature 2-8 °C (max. 1 month)
Concentration (ultrafiltration)	29.6.2016	29.6.2016	-	180 l ----> 55.75 l	-
Storage (2-8°C)	29.6.2016	30.6.2016	-	-	at temperature 2-8 °C (max. 5 months) or at ≤ -20°C (max. 5 months)

3.3. CREATION OF THE FINAL PRODUCT

3.3.1 Blending (batch no. 01 56 23)

Components	**Start date**	**End date**	**Bulk/batch number**	**Total volume**
Inactivated rabies virus, strain Vnukovo-32	30.6.2016	30.6.2016	63/2016/RVV	57 l
			64/2016/RVV	56 l
			66/2016/RVV	56 l
			67/2016/RVV	55.75 l
			-	-
			-	-
Aluminium hydroxide gel			5227	25 l
Thiomersal			000 667	0.25 l
Water for injection			-	-
Final bulk volume (min. 70 l – max. 1000 l)				
Storage (2-8°C)	30.6.2016	30.6.2016	01 56 23	190 l
Storage (2-8°C)	30.6.2016	22.7.2016	01 56 23	60 l

3.3.1.1 Vaccine composition (batch no. 01 56 23)

Component	Batch no.	Target concentration	Final concentration
Rabies virus, strain Vnukovo-32	63/2016/RVV	Glycoprotein content min. 8 IU/ml (final vaccine bulk)	18.13 IU/ml
	64/2016/RVV		
	66/2016/RVV		
	67/2016/RVV		
	-		
	-		
Aluminium hydroxide gel	5227	0.15 – 0.30 %	0.1724%
Thiomersal	000 667	0.0085 – 0.0115 %	0.0115 %

3.3.2 Filling (batch no. 01 56 23 A,B)

Final batch number	Filling date		Number or filled container	Volume filled
	start	end		
01 56 23 A	30.6.2016	1.7.2016	18 017 pcs	10.3 ml
01 56 23 B	22.7.2016	22.7.2016	5 252 pcs	10.3 ml

3.4. IN PROCESS CONTROLS

3.4.2. In process controls on live viral suspension

3.4.2.1. Rabies virus, strain Vnukovo-32, 63/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Titre	17.5.2016	19.5.2016	$10^{8.1}TCID_{50}/ml$	min. $10^{7.0}TCID_{50}/ml$	**Satisfy**
Sterility test	17.5.2016	31.5.2016	Sterile	Must be sterile	**Satisfy**

3.4.2.2. Rabies virus, strain Vnukovo-32, 64/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Titre	17.5.2016	19.5.2016	$10^{8.1}TCID_{50}/ml$	min. $10^{7.0}TCID_{50}/ml$	**Satisfy**
Sterility test	17.5.2016	31.5.2016	Sterile	Must be sterile	**Satisfy**

3.4.2.3. Rabies virus, strain Vnukovo-32, 66/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Titre	24.5.2016	26.5.2016	$10^{8.1}TCID_{50}/ml$	min. $10^{7.0}TCID_{50}/ml$	**Satisfy**
Sterility test	24.5.2016	7.6.2016	Sterile	Must be sterile	**Satisfy**

3.4.2.4. Rabies virus, strain Vnukovo-32, 67/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Titre	24.5.2016	26.5.2016	$10^{8.1}TCID_{50}/ml$	min. $10^{7.0}TCID_{50}/ml$	**Satisfy**
Sterility test	24.5.2016	7.6.2016	Sterile	Must be sterile	**Satisfy**

3.4.3. In process controls post – inactivation

3.4.3.1. Rabies virus, strain Vnukovo-32, 63/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Inactivation	18.5.2016	31.5.2016	Inactivated	No live virus must be detected	**Satisfy**
pH	18.5.2016	18.5.2016	7.62	7.2 – 7.8	**Satisfy**
Glycoprotein content	20.5.2016	20.5.2016	6.64 IU/ml	Min. 3.5 IU/ml	**Satisfy**
Glycoprotein content (after concentration)	29.6.2016	29.6.2016	19.06 IU/ml	Min. 10 IU/ml	**Satisfy**

3.4.3.2. Rabies virus, strain Vnukovo-32, 64/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Inactivation	18.5.2016	31.5.2016	inactivated	No live virus must be detected	**Satisfy**
pH	18.5.2016	18.5.2016	7.5	7.2 – 7.8	**Satisfy**
Glycoprotein content	20.5.2016	20.5.2016	6.44 IU/ml	Min. 3.5 IU/ml	**Satisfy**
Glycoprotein content (after concentration)	29.6.2016	29.6.2016	18.67 IU/ml	Min. 10 IU/ml	**Satisfy**

3.4.3.3. Rabies virus, strain Vnukovo-32, 66/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Inactivation	25.5.2016	7.6.2016	inactivated	No live virus must be detected	**Satisfy**
pH	25.5.2016	25.5.2016	7.47	7.2 – 7.8	**Satisfy**
Glycoprotein content	26.5.2016	26.5.2016	6.93 IU/ml	Min. 3.5 IU/ml	**Satisfy**
Glycoprotein content (after concentration)	29.6.2016	29.6.2016	19.47 IU/ml	Min. 10 IU/ml	**Satisfy**

3.4.3.4. Rabies virus, strain Vnukovo-32, 67/2016/RVV

Test	Start	End	Result	Thresholds	Conclusion
Inactivation	25.5.2016	7.6.2016	inactivated	No live virus must be detected	**Satisfy**
pH	25.5.2016	25.5.2016	7.45	7.2 – 7.8	**Satisfy**
Glycoprotein content	26.5.2016	26.5.2016	7.41 IU/ml	Min. 3.5 IU/ml	**Satisfy**
Glycoprotein content (after concentration)	29.6.2016	29.6.2016	23.49 IU/ml	Min. 10 IU/ml	**Satisfy**

3.4.4. In-process control on bulk vaccine after blending (batch no. 01 56 23)

Test	Start	End	Result	Thresholds	Conclusion
pH	30.6.2016	30.6.2016	7.52	6.5 – 8.5	**Satisfy**
Sterility test	30.6.2016	21.7.2016	complies	Must be sterile	**Satisfy**
Glycoprotein content (calculation in final vaccine bulk)	See 3.3.1.1 Vaccine composition				

4. FINAL PRODUCT TESTING - **Biocan R** suspension for injection (batch no.01 56 23A,B)

Test	Start	End	Result	Thresholds	Conclusion
Appearance	13.7.2016 29.7.2016	13.7.2016 (A) 29.7.2016 (B)	complies	Slight pink solution with fine sediment.	**Satisfy**
Extractable volume	13.7.2016 29.7.2016	13.7.2016 (A) 29.7.2016 (B)	10.5 ml 10.6 ml	min. 10 ml	**Satisfy**
Sterility test	4.7.2016 26.7.2016	25.7.2016 (A) 16.8.2016 (B)	Sterile	The vaccine must be sterile.	**Satisfy**
Potency test	1.7.2016	29.7.2016	6.46 IU/ml	Min. 2.0 IU/ml	**Satisfy**
Potency test	1.7.2016	20.7.2016	>2 IU (p=0.000)	Antibody titers in mice after vaccination with the product batches are significantly higher than the titers obtained by standard vaccine 2 IU (p≤0.05)	**Satisfy**
Inactivation test	1.7.2016	22.7.2016	complies	The vaccine must be free from live rabies virus.	**Satisfy**
Aluminium hydroxide content	13.7.2016	13.7.2016	1.5995 mg/ml	2.0 mg/ml (1.5 – 3.0)	**Satisfy**
Thiomersal content	13.7.2016	13.7.2016	0.106 mg/ml	0.1 mg/ml (0.085 – 0.115)	**Satisfy**
pH	13.7.2016 29.7.2016	13.7.2016 (A) 29.7.2016 (B)	7.65 7.62	Between 6.5 and 8.5	**Satisfy**
Air tightness	13.7.2016 29.7.2016	13.7.2016 (A) 29.7.2016 (B)	complies	The vials must be hermetically sealed.	**Satisfy**

5. CERTIFICATION BY THE MANUFACTURER

Certification by qualified person taking the overall responsibility for production and control of the product: **Biocan R** batch N° **01 56 23 A,B**

I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging and quality control in full compliance with the GMP requirements of the local regulatory Authority and with the specifications on the Marketing Authorization of the importing country. The batch processing, packing and analysis records were reviewed and found to be in compliance with GMP.

NAME: Nezvalová Hana, Mgr.

FUNCTION: Head of QC, QP

DATE: 17.8.2016

SIGNATURE: .....