Screening for the Eye Irritancy Potential using the Bovine Corneal Opacity and Permeability Assay

with

Ammonium Niobium Oxalate

Report

Version: Final

Study Completion Date: 06 FEB 2014

BSL BIOSERVICE Study No.: 136507

Sponsor:

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GLP zertifiziert

Akkreditiert durch Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten ZLG-P-986.96.01

1. Copy of the GLP Certificate

Bayerisches Landesamt für
Gesundheit und Lebensmittelsicherheit

GLP-Bescheinigung/Statement of GLP Compliance
(gemäß/according to § 19b Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EC at:

☒ Prüfeinrichtung/Test facility ☐ Prüfstandort/Test site

BSL BIOSERVICE
SCIENTIFIC LABORATORIES GMBH
BEHRINGSTRAßE 6-8
82152 PLANEGG

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/Areas of Expertise
(gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

Kategorie 2
Kategorie 3
Kategorie 9*
**Mikrobiologische Sicherheitsprüfungen; Wirksamkeitsprüfungen an Zellkulturen*

Datum der Inspektion/Date of Inspection
(Tag.Monat.Jahr/day.month.year)
03.- 04.07.2012

Die/Der genannte Prüfeinrichtung/Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

The above mentioned test facility/test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/ diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Based on the inspection report it can be confirmed, that this test facility/test site is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Erlangen, 22.01.2013

Dr. Peter Franke
Leitender Regierungsdirektor

2. Contents

3. List of Tables

4. Preface

4.1. Abbreviations

Art.	Artikel *(article)*
BCOP	Bovine Corneal Opacity and Permeability Assay
BGBl.	Bundesgesetzblatt *(Federal Law Gazette)*
Dipl.-Biol.	Diplom Biologe (*Biology Diploma*)
FBS	fetal bovine serum
GLP	Good Laboratory Practice
GmbH	Gesellschaft mit beschränkter Haftung *(company with limited liability)*
HBSS	Hanks' balanced salt solution
IVIS	*in vitro* irritation score
MEM	minimum essential medium
NaCl	sodium chloride
No.	number
Nr.	Nummer *(number)*
OECD	Organisation for Economic Cooperation and Development
Pen/Strep	penicillin/streptomycin
QA	Quality Assurance
QAU	Quality Assurance Unit
RPMI	Roswell Park Memorial Institute
SOP	Standard Operating Procedure

4.2. General

Sponsor:	CBMM Europe BV WTC H-Tower Zuidplein 96 1077 XV Amsterdam The Netherlands
Study Monitor:	Dr. Claudia Schäfer Dr. Knoell Consult GmbH Marie-Curie-Str. 8 51377 Leverkusen Germany
Test Facility:	BSL BIOSERVICE Scientific Laboratories GmbH Behringstraße 6/8 82152 Planegg Germany
BSL BIOSERVICE Study No.:	136507
Test Item:	Ammonium Niobium Oxalate
Title:	Screening for the Eye Irritancy Potential using the Bovine Corneal Opacity and Permeability Assay with Ammonium Niobium Oxalate

4.3. Project Staff

Study Director:	Dipl.-Biol. Roland Schmitz
Management:	Dr. Wolfram Riedel Dr. Angela Lutterbach Dr. Katrin Witschital
Head of Quality Assurance Unit:	Dipl.-Biol. Uwe Hamann

4.4. Schedule

Arrival of the Test Item:	21 May 2012
Study Initiation Date:	09 January 2014
Experimental Starting Date:	15 January 2014
Experimental Completion Date:	15 January 2014

5. Quality Assurance

5.1. GLP Compliance

This study was conducted to comply with:

Chemikaliengesetz ("Chemicals Act") of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on August 28, 2013 (BGBl. I S. 3498) [1].

Konsens-Dokument der Bund-Länder-Arbeitsgruppe Gute Laborpraxis ("Consensus Document of the National and Länder Working Party on Good Laboratory Practice") on the archiving and storage of records and materials, 5 May 1998 [2].

OECD Principles of Good Laboratory Practice (as revised in 1997); OECD Environmental Health and Safety Publications; Series on Principles of Good Laboratory Practice and Compliance Monitoring - Number 1. Environment Directorate, Organisation for Economic Co-operation and Development, Paris 1998 [3].

This study was assessed for compliance with the study plan and the Standard Operating Procedures of BSL BIOSERVICE. The study and/or the test facility were periodically inspected by the Quality Assurance Unit according to the corresponding SOPs. These inspections and audits were carried out by the Quality Assurance Unit, personnel independent of staff involved in the study. A signed quality assurance statement, listing all performed audits, is included in the report.

5.2. Guidelines

This study followed the procedures indicated by internal BSL BIOSERVICE SOPs and the following internationally accepted guidelines and recommendations:

OECD Guideline for the Testing of Chemicals, number 437 "Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants" (adopted: 26 July 2013) [4].

5.3. Archiving

The records, materials and specimen will be stored according to the GLP regulations for a period of 15 years.

The following records have to be stored according to the GLP regulations:

A copy of the final report, the study plan and a documentation of all raw data generated during the conduct of the study (documentation forms as well as any other notes of raw data, printouts of instruments and computers) and the correspondence with the sponsor concerning the study. Any document relating to the study will be discarded only with the prior consent of the sponsor.

The following materials and samples have to be stored according to the period of time specified in the GLP regulations:

A retain sample of the test item will be archived according to the GLP regulations, if possible, and will be discarded without the sponsor's prior consent.

Other materials and specimen have to be stored according to the GLP regulations and disposed after the respective archiving period with the sponsor's prior consent.

Unless otherwise agreed in writing, the remaining test item will be discarded three months after the release of the report.

6. Statement of Compliance

BSL BIOSERVICE Study No.:	136507
Test Item:	Ammonium Niobium Oxalate
Title:	Screening for the Eye Irritancy Potential using the Bovine Corneal Opacity and Permeability Assay with Ammonium Niobium Oxalate
Study Director:	Dipl.-Biol. Roland Schmitz

This study performed in the test facility BSL BIOSERVICE Scientific Laboratories GmbH was conducted in compliance with Good Laboratory Practice Regulations:

Chemikaliengesetz ("Chemicals Act") of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on August 28, 2013 (BGBl. I S. 3498) [1].

Konsens-Dokument der Bund-Länder-Arbeitsgruppe Gute Laborpraxis ("Consensus Document of the National and Länder Working Party on Good Laboratory Practice") on the archiving and storage of records and materials, 5 May 1998 [2].

"OECD Principles of Good Laboratory Practice (as revised in 1997)", Paris 1998 [3].

There were no circumstances that may have affected the quality or integrity of the study.

Study Director: Dipl.-Biol. Roland Schmitz

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Date: 06. Feb. 2014

This statement does not include the preliminary test.

7. Statement of the Quality Assurance Unit

BSL BIOSERVICE

Study No.:	136507
Test Item:	Ammonium Niobium Oxalate
Title:	Screening for the Eye Irritancy Potential using the Bovine Corneal Opacity and Permeability Assay with Ammonium Niobium Oxalate
Study Director:	Dipl.-Biol. Roland Schmitz

This report and the conduct of this study were inspected by the Quality Assurance Unit on the following dates:

Phases of QAU Inspections	Dates of QAU Inspections	Dates of Reports to the Study Director and Management
Audit Final Study Plan:	10 January 2014	10 January 2014
Audit Experimental Phase (study-based):	15 January 2014	15 January 2014
Audit Final Report:	06 FEB 2014	06 FEB 2014

This report reflects the raw data.

Member of the
Quality Assurance Unit:

.....

Print Name:

Date: 07 Feb 2014

8. Summary

8.1. Summary Results

The eye irritancy potential of Ammonium Niobium Oxalate was investigated in the bovine corneal opacity and permeability assay.

Preparation of the test item:	The test item was suspended with physiological saline 0.9% NaCl to gain a 20% concentration
Mean *in vitro* irritation score:	280.15

Classification:

☐	UN GHS No Category
☐	No prediction can be made
☒	UN GHS Category 1

The *in vitro* irritation score obtained with the positive control fell within the two standard deviations of the current historical mean and therefore this assay is considered to be valid.

8.2. Conclusion

According to the evaluation criteria the test item Ammonium Niobium Oxalate is classified into UN GHS Category 1.

9. Introduction

9.1. Justification for the Selection of the Test System

The Bovine Corneal Opacity and Permeability (BCOP) test method is an *in vitro* test method that can be used to classify substances as "ocular corrosives / severe irritants" and "non-irritants". The BCOP is recommended for use as part of a tiered-testing strategy for regulatory classification and labelling within a specific applicability domain. Test substances can be classified as ocular corrosives / severe irritants or non-irritants without further testing in rabbits [4].

To ensure test method integrity the data of the BCOP assay (Bovine Corneal Opacity and Permeability Assay), reference substances are tested in parallel to the test item.

10. Materials and Methods

10.1. Characterisation of the Test Item

The identity of the test item was inspected upon delivery at the test facility (e.g. test item name, batch no. and additional data were compared with the label) based on the following specifications provided by the sponsor.

Name:	**Ammonium Niobium Oxalate**
Batch No.:	AD/4663
Chemical Name:	Reaction mass of ammonium diaqua[bis(oxalate)]oxoniobate(1-)hydrate and ammonium hydrogen oxalate oxalic acid (1:1:1) dehydrate
Purity:	≥ 96%
Physical State:	powder
Colour:	white
Storage Conditions:	at room temperature
Expiry Date:	will be included in the report
Safety Precautions:	The routine hygienic procedures were sufficient to assure personnel health and safety.

10.2. Preparation of the Test Item

The test item was suspended with physiological saline 0.9% NaCl (see 10.3) to gain a 20% concentration.

10.3. Other Materials

Physiological saline 0.9% NaCl, Diprom, lot no. 13001-4, expiry date: 12/2015

Imidazole, Sigma, lot no. SLBC7446V, expiry date: 11/2014

RPMI 1640 without phenol red, Biochrom, lot no. 0207B, expiry date: 02/2015

Fetal bovine serum (FBS), PAA, lot no. A15112-2026, expiry date: 06/03/2014

L-glutamine, Gibco, lot no. 1319363, expiry date: 08/2014

Minimum essential medium (MEM) with phenol red (used for the rinsing of test substances only), Gibco, lot no. 1322539, expiry date: 04/2014

Hanks' balanced salt solution (HBSS) with Ca++ and Mg++, Gibco, lot no. 1379580, expiry date: 06/2015, containing penicillin/ streptomycin, PAA, lot no. P01013-2182, expiry date: 12/2014

Sodium fluorescein, Sigma, lot no. 079K0141V, expiry date: 03/2016

10.4. Test System

10.4.1. Preparation of the Corneas

The assay uses isolated corneas obtained as a by-product from animals freshly slaughtered at the abattoir A. Moksel AG, Buchloe.

On the test day, fresh eyes were collected from the slaughterhouse and were transported in HBSS containing Pen/Strep on ice to the laboratories. Immediately after arrival of the eyes, cornea preparation was initiated.

The eyes were carefully examined for defects and any defective eyes were discarded.

The tissue surrounding the eyeball was carefully pulled away and the cornea was excised leaving a 2 to 3 mm rim of sclera. The isolated corneas were stored in a petri dish containing HBSS. Before the corneas were mounted in corneal holders (MC2, Clermont, France) with the endothelial side against the O-ring of the posterior chamber, they had been visually examined for defects and any defective cornea had been discarded. The anterior chamber was then positioned on top of the cornea and tightened with screws. The chambers of the corneal holder were then filled with RPMI (without phenol red) containing 1% FBS and 2 mM L-glutamine (complete RPMI). The posterior chamber was always filled first. The corneas were incubated for one hour at 32 ± 1 °C in a water bath.

10.4.2. Calibration of the Opacitometer

The opacitometer had been switched on 15 min before the calibration procedure was started. Empty cornea holders were placed into the opacitometer and the readout was adjusted to zero using the "BAL"-turning knob. For calibration the polyester foil no. 1 was introduced into the test chamber and the readout was adjusted to 75 using the "CAL"-turning knob. To test the linearity of the measurement, two additional calibration foils, polyester foil no. 2 and polyester foil no. 3, were measured. For these, the opacitometer was supposed to display 150 and 225, respectively (± 3%). If this had not been the case, the calibration procedure would have had to be repeated. The calibration procedure was performed before each test and was documented in the raw data.

10.4.3. Treatment of the Corneas

After the equilibration period, the medium was removed from both chambers and replaced with fresh Complete RPMI. An initial opacity measurement was performed on each of the corneas using an opacitometer (MC2, Clermont, France). Three corneas with opacity readings approximately equivalent to the median opacity of all corneas were selected as negative-control corneas. The opacity of each cornea was read against an air-filled chamber and recorded. Corneas that have an initial opacity reading above 7 units were not dosed. The medium was removed from the anterior chamber and replaced with the test item or control.

750 µL of the test item preparation or the control substance was introduced into the anterior chamber (closed-chamber method). After 4 hours ± 5 minutes incubation at 32 ± 1 °C either the test substance or the control substance was removed and the epithelium washed at least three times with MEM (containing phenol red). Once the medium was free of test substance, the cornea was finally rinsed with complete RPMI (without phenol red). The anterior chamber was refilled with complete RPMI and an opacity measurement was performed.

After the opacity measurement the medium was removed from both chambers of the holder. The posterior chamber was refilled with fresh complete RPMI. 1 mL of a 5 mg/mL sodium fluorescein solution was added to the anterior chamber and the corneas were incubated for 90 minutes at 32 ± 1 °C. Then the medium from the posterior chamber was

removed and its optical density at 490 nm (OD490) was determined, using a spectrophotometer.

10.5. Test Groups

3 corneas for the test item

3 corneas as negative controls treated with physiological saline 0.9% NaCl

3 corneas as positive control treated with imidazole 20% in physiological saline 0.9% NaCl

The BCOP assay is considered to be valid if the *in vitro* irritation score obtained with the positive control falls within the two standard deviations of the current historical mean.

10.6. Evaluation of Results

The change in opacity for each cornea was calculated by subtracting the initial opacity reading from the final opacity reading. These values were corrected by subtracting from each the average change in opacity observed for the negative-control corneas. The mean opacity value for each treatment was calculated by averaging the corrected opacity values of each cornea for a given treatment.

The mean OD490 for the blank wells were calculated. The mean blank OD490 was subtracted from the OD490 of each well (corrected OD490). Any dilutions that were made to bring the OD490 values into the linear range of the spectrophotometer (OD490 should be less than 1.500), were taken into account by multiplying the OD490 value of the dilution by the dilution factor. The final-corrected OD490 of the test article and the positive control were calculated by subtracting the average corrected OD490 of the negative control corneas from the corrected OD490 value of each treated cornea:

Final-corrected OD490 = (OD490 – mean blank OD490) – average-corrected negative control OD490

The mean OD490 value of each treatment group was calculated by averaging the final corrected OD490 values of the treated corneas for that treatment condition.

The following formula was used to determine the *in vitro* irritation score:

In vitro irritation score (IVIS) = mean opacity value + (15 x mean OD490 value)

The IVIS cut-off values for identifying test substances as inducing serious eye damage (UN GHS Category 1) and test substances not requiring classification for eye irritation or serious eye damage (UN GHS No Category) are given in Table 1:

Table 1: Evaluation of the BCOP Assay

Mean Score	UN GHS
≤ 3	No Category
> 3; ≤ 55	No prediction can be made
> 55	Category 1

An identification of test substances that should be classified as irritating to eyes (UN GHS Category 2 or Category 2A) or test substances that should be classified as mildly irritating to eyes (UN GHS Category 2B) cannot be made.

For this purpose further testing with another suitable method is required.

11. Deviations from the Study Plan

There were no deviations from the study plan.

12. Results

The eye irritancy potential of Ammonium Niobium Oxalate was investigated in the bovine corneal opacity and permeability assay.

The test item was suspended with physiological saline 0.9% NaCl to gain a 20% concentration.

The following mean *in vitro* irritation score was calculated:

280.15

Therefore the test item was classified into UN GHS Category 1.

The *in vitro* irritation score obtained with the positive control fell within the two standard deviations of the current historical mean and therefore this assay is considered to be valid. The negative control responses resulted in opacity and permeability values that are less than the established upper limits for background opacity and permeability values for bovine corneas treated with the respective negative control.

For detailed data see Tables 2 - 4 in the appendix.

13. Conclusion

According to the evaluation criteria the test item Ammonium Niobium Oxalate is classified into UN GHS Category 1.

14. Distribution of the Report

1 original (paper):	Sponsor
1 copy (paper):	BSL BIOSERVICE
1 copy (electronic):	Sponsor

15. References

15.1. Internal BSL BIOSERVICE SOPs

Standard Operating Procedures (SOPs), No. 11-8-2

15.2. Literature and Guidelines

[1] Chemikaliengesetz ("Chemicals Act") of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on August 28, 2013 (BGBl. I S. 3498)

[2] Konsens-Dokument der Bund-Länder-Arbeitsgruppe Gute Laborpraxis ("Consensus Document of the National and Länder Working Party on Good Laboratory Practice") on the archiving and storage of records and materials, 5 May 1998

[3] OECD Principles of Good Laboratory Practice (as revised in 1997); OECD Environmental Health and Safety Publications; Series on Principles of Good Laboratory Practice and Compliance Monitoring - Number 1. Environment Directorate, Organisation for Economic Co-operation and Development, Paris 1998

[4] OECD Guideline for the Testing of Chemicals, number 437 "Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants" (adopted: 26 July 2013)

[5] GHS - Globally Harmonized System of Classification and Labelling of Chemicals. Fifth revised edition, United Nations. New York / Geneva, 2013

[6] Gautheron, P, Dukic, M., Alix, D, Sina, J.F (1992) Bovine Corneal Opacity and Permeability Test: An *in vitro* Assay of Ocular Irritancy. Fundamental and Applied Toxicology 18:442-449

[7] Sina, J.F., Galer, D.M., Sussman, R.G., Gautheron, P.D., Sargent, E.V., Leong, B., Shah, P.V., Curren, R.D., Miller, K. (1995) A collaborative evaluation of seven alternatives to the Draize eye irritation test using pharmaceutical intermediates. Fundamental and Aplied Toxicology 26:20-31

[8] Vanparys, Ph., Deknudt, Gh., Sysmans, M., Teuns, G., Coussement, W., Van Cauteren, H. (1994) Evaluation of the bovine opacity-permeability assay as an in vitro alternative to the Draize eye irritation test. Toxicol. in vitro 7, 471-476

16. Appendix

16.1. Appendix 1 – Individual Data

Table 2: Opacity

Cornea No.	Test Item	Initial Opacity	Final Opacity	Change of Opacity Value	Corrected Opacity Value
1	Negative Control	3	4	1	
2		3	2	-1	
3		3	2	-1	
MV		3.00	2.67	-0.33	
4	Positive Control	4	137	133	133.33
5		4	151	147	147.33
6		4	153	149	149.33
MV		4.00	147.00	143.00	**143.33**
7	Test Item	3	330	327	327.33
8		3	251	248	248.33
9		3	268	265	265.33
MV		3.00	283.00	280.00	**280.33**

MV = mean value

Table 3: Permeability

Cornea No.	Test Item	OD490	Corrected OD490 Value
1	Negative Control	0.104	
2		0.120	
3		0.102	
MV		**0.109**	
4	Positive Control	2.048	1.939
5		2.036	1.927
6		1.999	1.890
MV		**2.028**	**1.919**
7	Test Item	0.134	0.025
8		0.110	0.001
9		0.046	-0.063
MV		**0.097**	**-0.012**

MV = mean value

Table 4: *In Vitro* Irritation Score

Cornea No.	Test Item	Change of Opacity Value	Corrected OD490 Value	IVIS
1	Negative Control	1.00	0.104	
2		-1.00	0.120	
3		-1.00	0.102	
MV		**-0.33**	**0.109**	**1.30**

Cornea No.	Test Item	Corrected Opacity Value	Corrected OD490 Value	IVIS
4	Positive Control	133.33	1.939	
5		147.33	1.927	
6		149.33	1.890	
MV		**143.33**	**1.919**	**172.12**
7	Test Item	327.33	0.025	
8		248.33	0.001	
9		265.33	-0.063	
MV		**280.33**	**-0.012**	**280.15**

MV = mean value

16.2. Appendix 2– Substance Identity Sheet

knoell

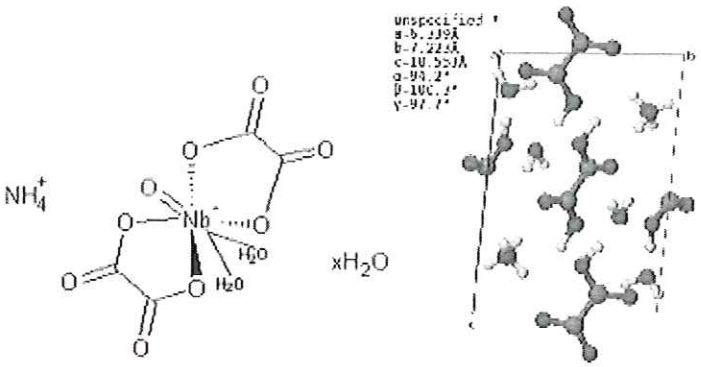
1. **Substance identity of ANO (CBMM)**

The substance ANO (Ammonium Niobium Oxalate, Sponsor CBMM) was examined. The following data according substance identity have to be indicated on "test item" in the study reports.

Test item:	ANO (common name)
Batch / Lot number:	AD/4663
Chemical name:	**Reaction mass of ammonium diaqua[bis(oxalate)]oxoniobate(1-) hydrate and ammonium hydrogen oxalate oxalic acid (1:1:1) dehydrate**
Type of substance:	Multi-constituent substance
Purity:	≥ 96%
Molecular weight range:	339.012 - 446.261

The reported molecular weight (MW) is indicated for the reaction mass, of which the constituent 1 contains crystal water x ranged from 0 to 8 ($NH_4[NbO(C_2O_4)_2 \cdot 2H_2O] \cdot xH_2O$). Also the MW of 339.012 refers to the constituent 1 (x=0) and 466.261 to the constituent 2.

Structural formula:



Main constituents:
Ca. 70% (68-74% (w/w)) constituent 1: $(NH_4[NbO(C_2O_4)_2 \cdot 2H_2O] \cdot xH_2O)$; x=0-8

Ca. 27% (24-28% (w/w)) constituent 2: ($NH_4(C_2HO_4) \cdot (C_2H_2O_4) \cdot 2(H_2O)$)

Impurities:
Ca. 2.5% (1-3% (w/w)) free water
Ca.0.5% (0.1-1% (w/w)) organic and inorganic impurities (Na, K, Cl and SO4, as well as possible small quantity of reaction residue of oxalate and ammonium)

Constituent 1 ($NH_4[NbO(C_2O_4)_2 \cdot 2H_2O] \cdot xH_2O$); x=0-8
IUPAC name: Ammonium oxobis(ethanedioato) bisniobate(V) hydrates
Molecular formula: C4H8NNbO11.xH2O, x= 0 – 8
Molecular weight range: 339.012 - 483.134 (MW range is calculated for crystal water range x= 0-8)

Constituent 2 ($NH_4(C_2HO_4) \cdot (C_2H_2O_4) \cdot 2H_2O$)
IUPAC name: Ammonium hydrogen ethanedioate ethanedioic acid dehydrate
Molecular formula: C8H9N2O16.4H2O
Molecular weight: 466.261

Appearance: white powder