Investigational Medicinal Product Dossier (IMPD)

Cysteamine Bitartrate (NM002/Nylexa®)

Version21.0 dated 1318 Aug Dec 2021

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1. Introduction

This IMP dossier supports the cysteamine bitartrate Domain-Specific Appendix (DSA) of the REMAP-CAP clinical trial protocol entitled:

" REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia", Cysteamine Domain-Specific Appendix Version 1 dated 21st June 2021 (EudraCT Number: 2015-002340-14).

The IMPD contains data on the drug substance and investigational medicinal product.

2. Information on the chemical and pharmaceutical quality concerning investigational medicinal products in clinical trials

2.1.S Drug substance

Cysteamine bitartrate is an aminothiol salt that was approved first in 1994 by US-FDA and followed by approval in 1977 by EMA for the treatment of nephropathic cystinosis in oral form. Cysteamine ophthalmic solution was approved by both FDA and EMA in the year 2012 and 2017 respectively for the treatment of corneal cystine crystal accumulation in patients with cystinosis. The marketing authorisation details of the products using the active substance, cysteamine bitartrate are provided in **Table 1** below.

NovaBiotics has been granted orphan drug designation for cysteamine bitartrate by both EMA (2011) and FDA (2014) for the treatment of cystic fibrosis. NovaBiotics was also granted Fast Track Designation status for cysteamine bitartrate for the treatment of pulmonary exacerbations in cystic fibrosis by FDA in February 2018.

	Approved by both EMA & FDA			FDA
Brand Name	Cystagon	Procysbi	Cystadrops	Cystaran
Generic name	Cysteamine bitartrate	Cysteamine bitartrate	Cysteamine hydrochloride	Cysteamine hydrochloride
Therapeutic area	Nephropathic cystinosis	Nephropathic cystinosis	Ocular cystinosis	Ocular cystinosis
Active Substance	Mercaptamine bitartrate	Mercaptamine bitartrate	Mercaptamine hydrochloride	Cysteamine hydrochloride
Dosage form	50 and 150 mg capsules	25 and 75 mg capsules	Ophthalmic solution: 0.37%, containing 3.8 mg/mL of cysteamine	Ophthalmic solution 0.44%, containing 4.4 mg/mL of cysteamine
ATC Code	A16AA04	A16AA04	S01XA21	S01XA21
Date approved by FDA	15 Aug 1994	30 April 2013	25 Aug 2020	October 2, 2012
Date approved in EU	23 June 1997	5 September 2013	19 January 2017	-
EU Marketing authorisation number	EU/1/97/039/001 EU/1/97/039/002 EU/1/97/039/003 EU/1/97/039/004	EU/1/13/861/001 EU/1/13/861/002	EU/1/15/1049/001 EU/1/15/1049/002	-
US FDA New Drug Application	NDA: 020392	NDA: 213491 & NDA: 203389	NDA: 211302	NDA: 200740
Marketing authorization holder	Recordati Rare Diseases	Chiesi Farmaceutici S.p.A*	Recordati Rare Diseases	Sigma-Tau Pharmaceutical, Inc.

Table 1: Marketing authorisation details of the products using the active substance, cysteamine bitartrate from the EMA and FDA regions.

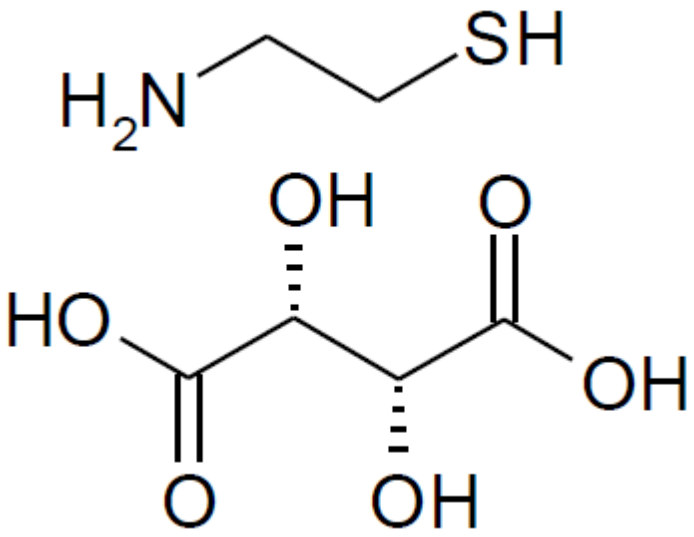
**In February 2017, Raptor Pharmaceuticals Europe B.V changed name to Horizon Pharma Europe B.V. In November 2017, Horizon Phama Europe B.V. changed name to Chiesi Orphan B.V. The sponsorship was transferred to Chiesi Farmaceutici S.p.A., Italy, in May 2018.*

2.1.S.1 General information

2.1.S.1.1 Nomenclature

International non-proprietary name (INN) or common name	Mercaptamine bitartrate
Compendial Name	Non-pharmacopoeial. Not described in U.S pharmacopeia, European and British pharmacopoeia
IUPAC	• 2-aminoethanethiol • 2,3-dihydroxybutanedioic acid
Chemical Name	• Ethanethiol,2-amino, [R-(R*,R*)] • 2,3-dihydroxy-butanedioate (1:1) salt • Mercaptamine bitartrate • 2-aminoethanethiol bitartrate
BANM, USAN	Cysteamine bitartrate
CAS Number	27761-19-9
COMPANY CODE (Cambrex Profarmaco Milano S.r.l.)	123

2.1.S.1.2 Structure



Molecular formula: $C_2H_7NS * C_4H_6O_6$

Molecular mass: 227.24

2.1.S.1.3 General properties

Description	White crystalline powder with characteristics sulfide-like odour
Physical appearance	White crystalline powder
Solubility	Freely soluble in water and methanol (at 40°C); insoluble in organic solvents
Dissociation constants	Acid pKa 8.19; Basic pKa 10.61
Partition coefficient	Log Kow = - 0.20 [Cysteamine (base)] Log Kow < - 1.0 (Cysteamine bitartrate)
Melting range	about 118 - 121°C
Hygroscopicity	Highly hygroscopic powder
Reactivity	Rapidly oxidizes in atmosphere conditions to Cystamine; Stored under nitrogen atmosphere to avoid degradation.
Optical rotation	Cysteamine bitartrate does not show optical activity
Polymorphism	Cambrex Profarmaco Milano current production of cysteamine bitartrate is consistent from the point of view of the polymorphic form: the IR spectra, the DSC thermograms and the X-ray diffraction patterns of different lots are perfectly superimposable. See Section **2.1.S.3.1** "Elucidation of structure and other characteristics – Polymorphism" for the detailed description of the study.

2.1.S.2 Manufacture

2.1.S.2.1 Manufacturer(s)

ADMINISTRATIVE ADDRESS, REGISTERED OFFICE, AND MANUFACTURING FACILITY

Cambrex Profarmaco Milano S.r.l.
Via Curiel, 34
20067 Paullo, Milano – Italy
Telephone: +39 02 9062601
Fax: +39 02 90630995

D-U-N-S Number (Data Universal Numbering System): 43-805-1401
FEI number (Facility Establishment Identifier): 3003723076

RESPONSIBLE OFFICIAL
Dr. Aldo Magnini
Managing Director
Via Curiel, 34
20067 Paullo, Milano – Italy

US AGENT
Mark TePaske
Sr. Director, Global Regulatory Affairs, Quality and Compliance
Cambrex Corporation
1205 11th Street
Charles City, IA 50616
Telephone: 1-(641)257-1026
Fax: 1-(641)228-4152

IN-HOUSE STABILITY TESTING LABORATORY
Cambrex Profarmaco Milano S.r.l
Via Curiel, 34
20067 Paullo (Milano) – Italy

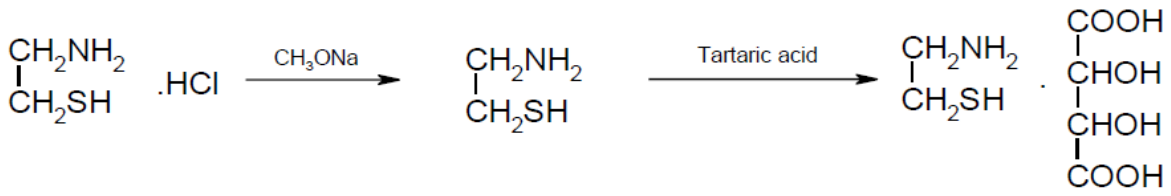
ALTERNATIVE STABILITY TESTING LABORATORY (*)
PRC (Pharma Research Centre) TICINUM LAB
Via Bovio, 6
28100 NOVARA, Italy

D-U-N-S Number: 43-733-9604
FEI number (Facility Establishment Identifier): 3005987780
(*) The description of the external stability testing laboratory is included in section 3.2.S.7.1.

WAREHOUSE FOR THE STORAGE OF API UNDER REFRIGERATED CONDITIONS
NEOLOGISTICA SRL
Largo Boccioni 1
21040 Origgio (Milano)
Italy

2.1.S.2.1 Description of manufacturing process and process controls

The scheme of the synthesis of CYSTEAMINE BITARTRATE is:



Solvents used in the manufacturing process
Ethanol (Final Purification Solvent)

Metal catalysts used in the manufacturing process
None

2.1.S.2.2 Control of materials

The raw materials used in the manufacturing process of cysteamine bitartrate and their specifications are confidential information of the API manufacturer, Cambrex Profarmaco Milano S.r.l.. Therefore, a detailed manufacturing information would be provided to the assessor directly by Cambrex Profarmaco Milano S.r.l. as and when required by the authorities.

2.1.S.2.3 Control of critical steps and intermediates

This information would be provided to the assessor directly by Cambrex Profarmaco Milano S.r.l. as and when required by the authorities.

2.1.S.2.4 Process validation

Not applicable for substances to be used in clinical trials.

2.1.S.2.5 Manufacturing process development

This information would be provided to the assessor directly by Cambrex Profarmaco Milano S.r.l. as and when required by the authorities.

2.1.S.3 Characterisation

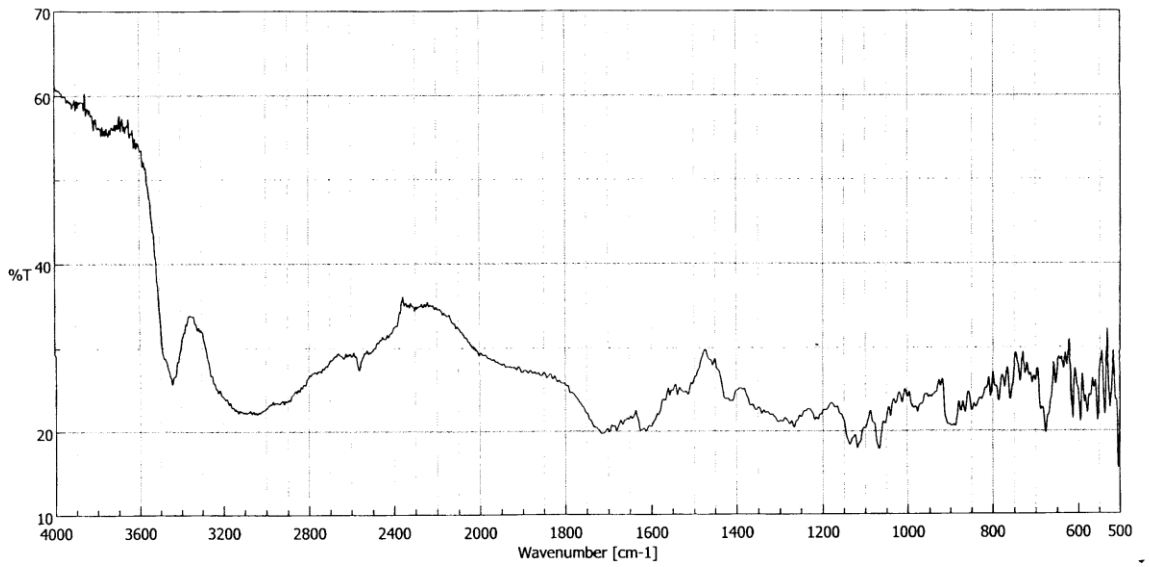
2.1.S.3.1 Elucidation of structure and other characteristics

Spectral analysis

The elucidation of the chemical structure of cysteamine bitartrate is based on the IR, NMR, MS spectra and Elemental analysis.

IR spectrum

The Infrared Absorption Spectrum of cysteamine bitartrate in KBr when run on a Jasco FT-IR 420 Spectrometer exhibits maxima as shown on the attached spectrum.



^{1}H NMR spectrum

The Nuclear Magnetic Resonance Spectrum of cysteamine bitartrate in D_2O was recorded on EM360-60MHz NMR Spectrometer. The chemical shifts and spectral assignments of the protons are reported in **Table 2** below.

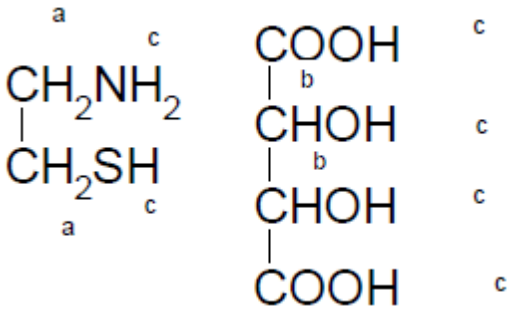
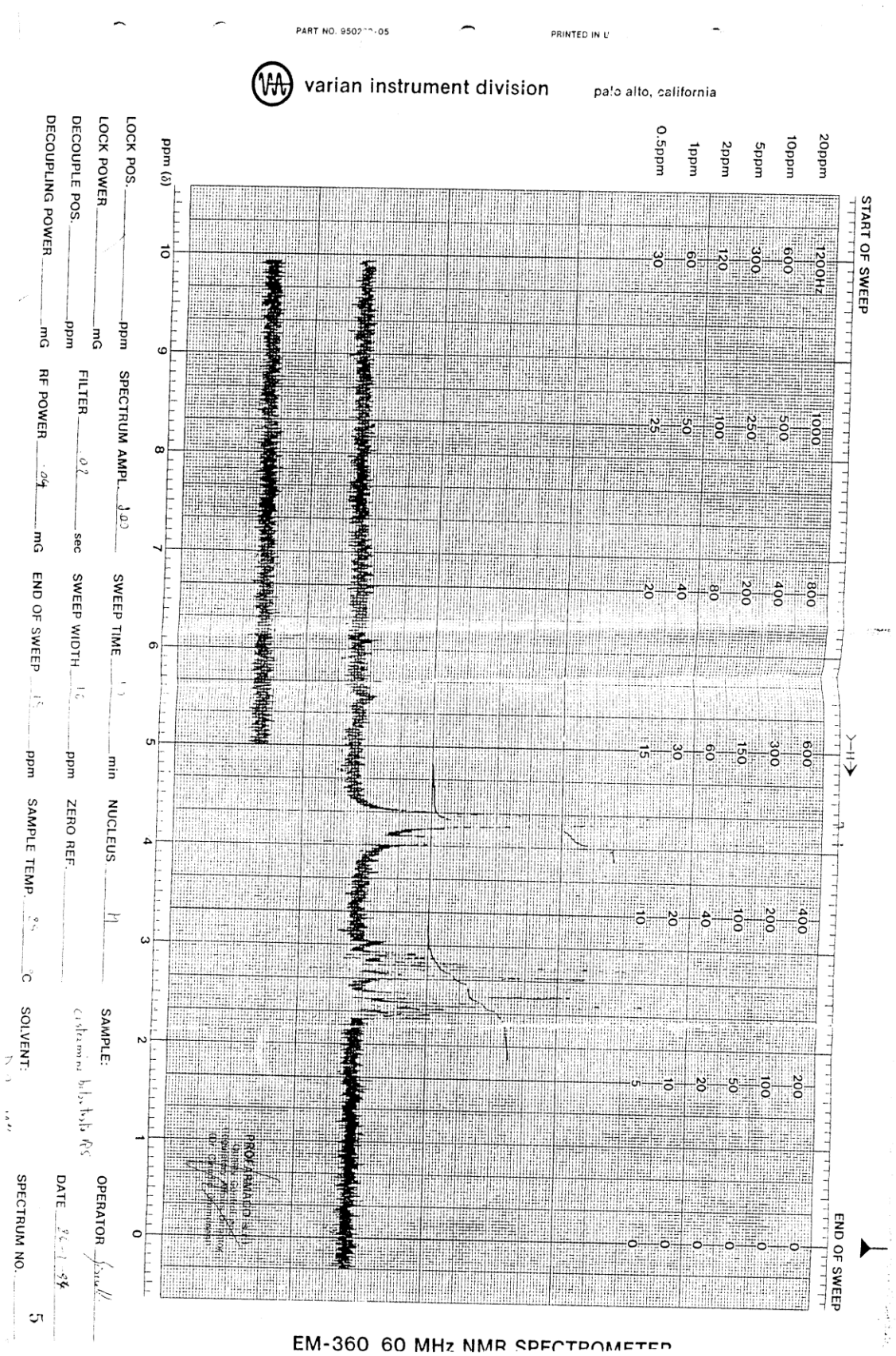


Table 2

Assignments	Chem. Shifts (ppm)	N° of hydrogens
a	2.3-2.9	4H
b	4.1	2H
c	4.3	7H

NMR spectrum is provided in the following page.


varian instrument division
palo alto, california
START OF SWEEP
END OF SWEEP
ppm (δ)
LOCK POS.
LOCK POWER
DECOUPLE POS.
DECOUPLING POWER
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SAMPLE:
OPERATOR
DATE
SOLVENT:
SPECTRUM NO.
EM-360 60 MHz NMR SPECTROMETER

^{13}C NMR spectrum

The NMR 13C spectrum of cysteamine bitartrate in D3O was recorded on BRUKER AC300. The chemical shifts and spectral assignments are reported in the **Table 3** below.

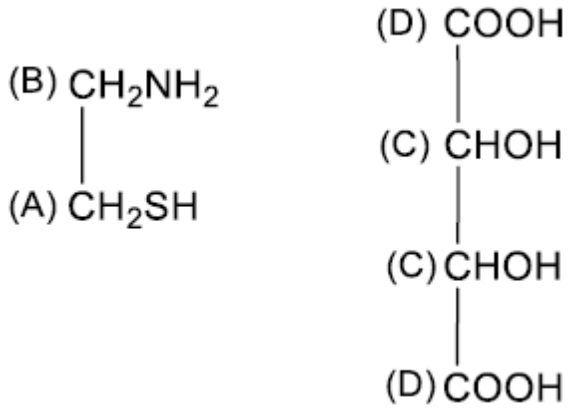
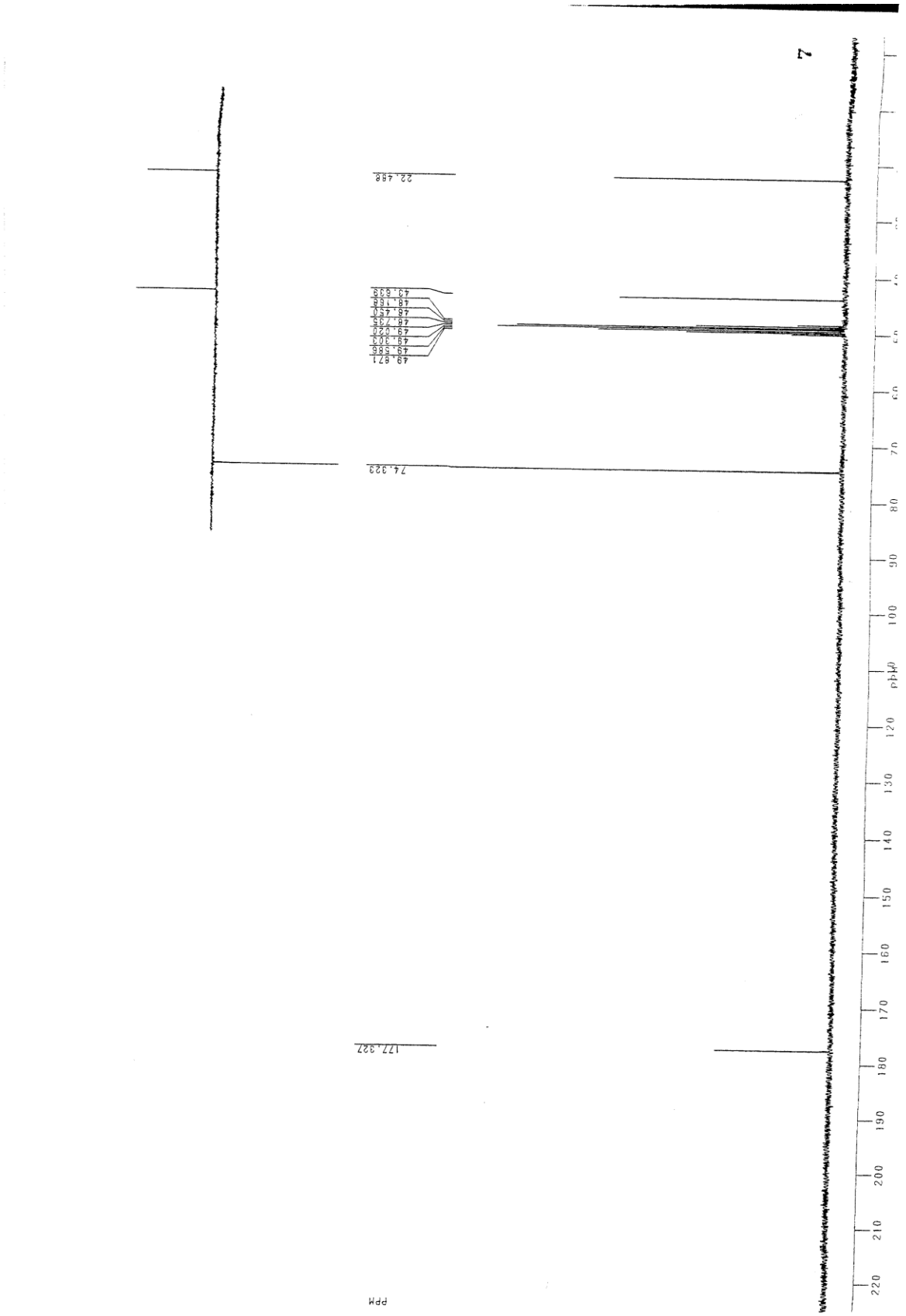


Table 3

Assignments	Chem. Shifts (ppm)
A	22.48
B	43.64
C	74.32
D	177.32

NMR spectrum is provided in the following page.


22.488
43.639
48.168
46.436
46.735
49.027
49.307
49.586
49.871
74.323
127.227
PPM
7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

MS spectrum

The Mass spectrum of cysteamine bitartrate in Methanol was recorded using a FINNIGAN INCOS 50 instrument. The fragmentation peaks in **Table 4** conform to the proposed structure:

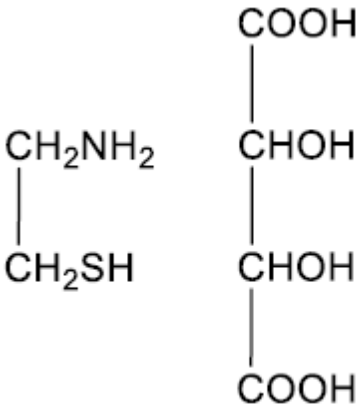
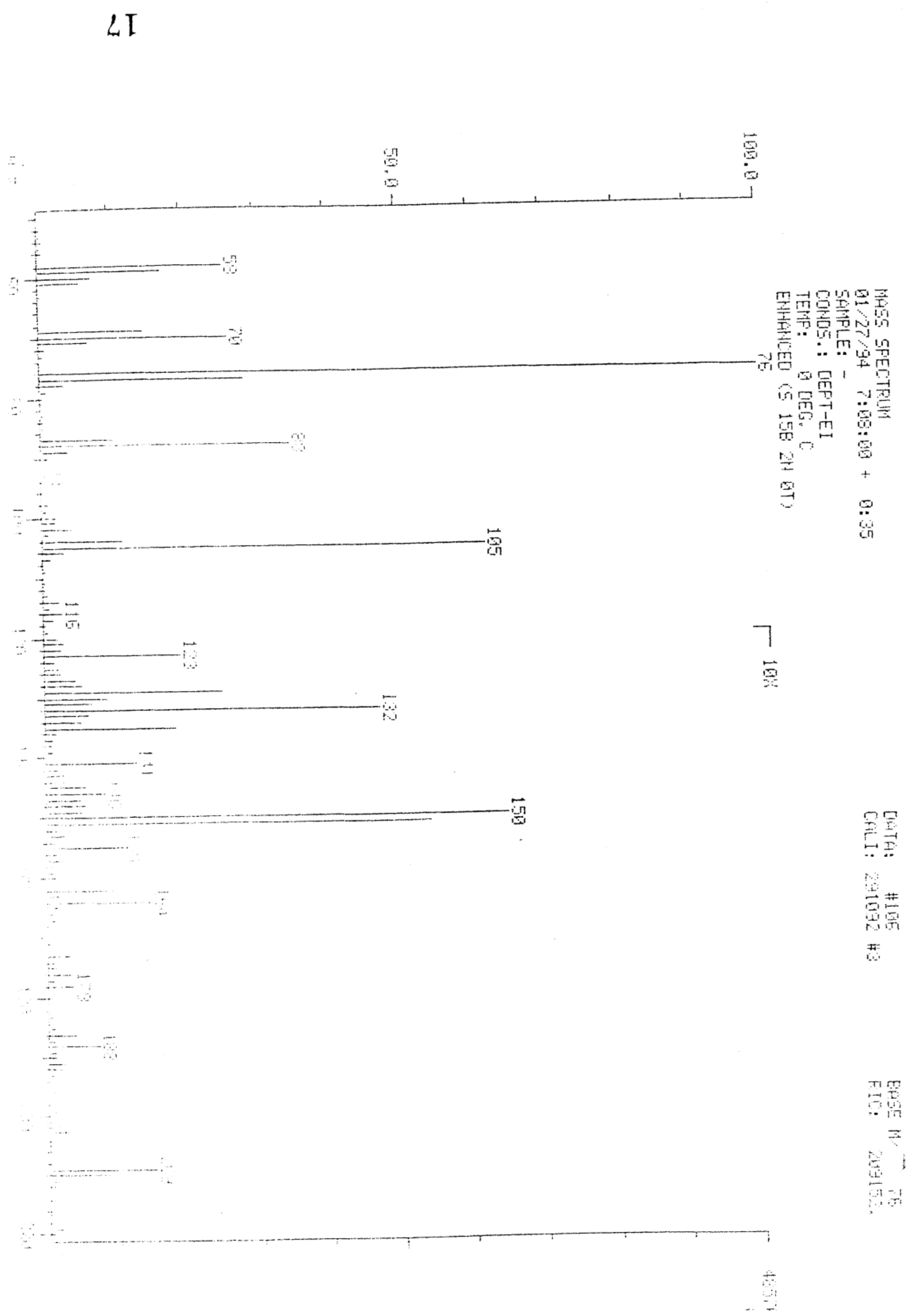


Table 4

Attribution	**m/z**
MW-H_2O	209
Peak of tartaric acid	150
150- H2O	132
150-COOH	105
HSCH2CH2NH2	76


MASS SPECTRUM
01/27/94 7:08:00 + 0:35
SAMPLE: -
CONDS.: DEPT-EI
TEMP: 0 DEG. C
ENHANCED (S 15B 2N 0T)
DATA: #106
CALI: 291092 #3
100.0
50.0
10X
58
70
76
88
105
116
123
132
150

Elemental analysis

The results of the elemental analysis of cysteamine bitartrate agree with the proposed structure, as reported in **Table 5** below.

Table 5

	% C	**% H**	**%N**	**%S**
% theoretical	31.7%	5.72%	6.16%	14.09%
% experimental	31.76%	5.76%	6.12%	14.01%

Potential isomerism

Cysteamine bitartrate does not show optical activity.

Polymorphism

In order to examine the polymorphism of the active ingredient cysteamine bitartrate, a deep study was conducted to demonstrate the consistency of the CAMBREX PROFARMACO MILANO manufacturing process from the point of view of the crystalline form.

Initially three different lots (lot #650101; #650202; #650303) of cysteamine bitartrate active ingredient had been examined by using the Infrared Spectrophotometry (IR), the Differential Scanning Calorimetry (DSC), the Thermal Gravimetric Analysis and the X-Ray Powder Diffraction (XRPD).

In parallel, the possibility of obtaining potential polymorphs of cysteamine bitartrate by crystallization of one of the previous lots has been evaluated so the cysteamine bitartrate active ingredient has been crystallized from different solvents and the resulting powders have been characterized by IR, DSC, TGA and XRPD.

CAMBREX PROFARMACO MILANO current production of cysteamine bitartrate is consistent from the point of view of the polymorphic form: the IR spectra, the DSC thermograms and the X-ray diffraction patterns are superimposable. All techniques used for its characterization have given totally comparable results for the lots examined.

2.1.S.3.2 Impurities

Potential impurities and degradation products

The specified impurities for cysteamine bitartrate are the following:

- CYSTAMINE NMT 2.0%
(potentiometric titration)

The limit for this impurity is reported on the Certificate of analysis.

The levels of the impurity in the batches of cysteamine bitartrate recently manufactured are reported in **Section 2.1.S.4.4** (Batch analysis).

Description of specified impurities

Cystamine

NH2-CH2-CH2-S-S-CH2-CH2-NH2

This is an impurity coming from the oxidation of cysteamine. It can be considered a synthesis as well as a degradation impurity.

Degradation products

CYSTAMINE can be also considered a degradation product coming from the oxidation of cysteamine bitartrate.

Residual solvents

The organic solvent used during the synthesis of cysteamine bitartrate is:

- Ethanol *(Final Purification Solvent*)

Ethanol (Class 3 solvent) is controlled on the final API by Loss on Drying NMT 0.5%.

Elemental Impurities (ICH Q3D)

1) With reference to metals used in the manufacturing process:

- No metal catalysts are used during the manufacturing process of cysteamine bitartrate.

2) With reference to metals with high probability of occurrence across different sources:

- According to Guideline ICH Q3D, Cambrex Profarmaco Milano has performed risk assessment on all its manufacturing processes to identify the most critical active ingredients to be analysed for the content of elemental impurities. A screening of potential sources of elemental impurities was performed and the following metals with ubiquitous nature were chosen for the study: Cd, Pb, As, Hg (Class 1), Ni, Co, V (Class 2A), Li, Sb, Ba, Mo, Cu, Sn, Cr (Class 3).

- 5 APIs have been identified from the risk assessment as the most critical products, and on these five active ingredients we have verified absence of contamination through validated ICP-MS methods.
- The methods were validated considering as LOQ limit the 30% of ICH parenteral limit Option 1.
- From the results obtained on the 5 risk assessment APIs, we confirm that all metals were never detected in the batches analysed (3 batches for each API) above LOQ.

Risk Management Summary is reported in the **Table** below:

Element	**Class**	**Intentionally added? ***	**Considered in risk management?**	**Conclusion****
Cd	1	NO	YES	Absent
Pb	1	NO	YES	Absent
As	1	NO	YES	Absent
Hg	1	NO	YES	Absent
Co	2A	NO	YES	Absent
V	2A	NO	YES	Absent
Ni	2A	NO	YES	Absent
Tl	2B	NO	NO	Absent
Au	2B	NO	NO	Absent
Pd	2B	NO	NO	Absent
Ir	2B	NO	NO	Absent
Os	2B	NO	NO	Absent
Rh	2B	NO	NO	Absent
Ru	2B	NO	NO	Absent
Se	2B	NO	NO	Absent
Ag	2B	NO	NO	Absent
Pt	2B	NO	NO	Absent
Li	3	NO	YES	Absent
Sb	3	NO	YES	Absent
Ba	3	NO	YES	Absent
Mo	3	NO	YES	Absent
Cu	3	NO	YES	Absent
Sn	3	NO	YES	Absent
Cr	3	NO	YES	Absent

** Yes / No; ** Absent (below 30% ICH Q3D Option 1 parenteral limit)*

Conclusions

According to the results of the Risk Assessment, Cambrex Profarmaco Milano S.r.l. can consider that elemental impurities are not present in cysteamine bitartrate above 30% of ICH Guideline Q3D Option 1 parenteral limit.

2.1.S.4 Control of drug substance

2.1.S.4.1 Specification(s)

Cysteamine bitartrate (M) manufactured by Cambrex Profarmaco Milano S.r.l. is controlled for compliance with the following specifications.

TSN°	Product Name	Date
010.001	Cysteamine bitartrate (M)	05/2013 Revised on 10/2019

Requirements

Formula	M.W.	CAS n°
$C_2H_7NS * C_4H_6O_6$	227.2	27761-19-9

TEST	SPECIFICATIN/LIMITS	N°. Ed. Rev
Description	White crystalline powder with characteristics sulfide-like odour	1.0601
Solubility (water)	Clear solution	2.0601
Colour (water)	Abs. 420 nm NMT 0.100	3.0601
Identification (IR)	Conforms to standard	4.0601
Identification (Melting Range)	118 - 121°C	5.0601
Residue on ignition	NMT 0.1%	6.0801
Loss on drying	NMT 0.5%	7.0601
Chlorides	NMT 100 ppm	8.0601
Assay by titration	97.0 – 102.0% (on dried basis)	9.0601
Free Tartaric Acid	NMT 1.0%	10.0601
Cystamine content	NMT 2.0%	11.0701
Particle Size	NLT 50% < 150 microns NLT 90% < 450 microns	12.0601

Retest date: 9 months; Storage conditions: triplex aluminium, not vacuum-packed, 5°C +/- 3°C. (COA – 010.004).

2.1.S.4.2 Analytical procedures

The following analytical specifications were followed by Cambrex Profarmaco Milano S.r.l.

DESCRIPTION

Description	White crystalline powder	1.0601

Method: Visual inspection

Distribute the powder on a white surface and visual-inspect under a source of light.

- No foreign matters must be present
- The product is a white crystalline powder, with characteristics sulfide-like odour

SOLUBILITY

Solubility (water)	Clear solution	2.0601

Method: House method

Water (10% solution)

- Dissolve 1g of product in 10 mL of water

The solution must be clear and without presence of foreign matters.

COLOUR

Colour (water)	NMT 0.100 (Abs. 420 nm)	3.0601

Equipment

UV Spectrophotometer, Jasco V-530 or similar, 1 cm cell

Procedure (2% solution)

1. Dissolve 1 g of product in 50 mL of water
2. Reset the UV to zero using water at 420 nm
3. Read the absorbance of the solution at 420 nm

$$Absorbance_{420} < 0.100$$

IDENTIFICATION

Identification (IR)	Conforms to standard	4.0601

Method: USP <197 K>

Equipment

IR Spectrophotometer, Jasco FTIR 420 or similar

Procedure

1. Mix about 5 mg of cysteamine bitartrate with 500 mg of dry, finely powdered KBr
2. Put the mixture in the proper holder in the IR spectrophotometer

The IR exhibits maxima at the similar wavenumbers and with similar relative intensities as to the reference spectrum.

IDENTIFICATION (MELTING RANGE)

Identification (Melting Range)	118 - 121°C	5.0601

Equipment

Buchi B-545 or similar

Procedure

1. Introduce a sufficient quantity of product into a capillary tube
2. Compact the product in order to obtain about 4-6 mm
3. Raise the temperature of the bath to about 10°C below the melting point (108°C)
4. Adjust the rate of heating to 1°C per minute
5. Introduce the capillary when the temp. is about 5°C below the melting point (113°C)

RESIDUE ON IGNITION

Residue on ignition	NMT 0.1%	6.0801

Method: USP <281>

Equipment

- Balance Mettler Toledo AG 245 or similar
- Muffle

Procedure

1. Weigh accurately 1 g of the product to be examined in a suitable crucible, that previously has been ignited, cooled, and weighed
2. Heat gently at first until the substance is thoroughly charred
3. Cool, then moisten the residue with 2 mL of 98% conc. Sulphuric acid
4. Heat gently until white fumes are no longer evolved and ignite at 600°C +/- 50°C until carbon is consumed.

Before weighing, let the product cool to room temperature into a desiccator.

Calculations

Product weight = Gross weight (before ignition) – Crucible tare weight
Residue = Gross weight (after ignition) – Crucible tare weight

$$\text{Residue on ignition \%} = \frac{\text{Residue} \times 100}{\text{Product weight}}$$

LOSS ON DRYING

Loss on drying	NMT 0.5%	7.0601

Method: USP <731>

Equipment

- Balance Mettler Toledo AG 245 or similar, Oven Heraeus or similar

Procedure

1. Tare an aluminium plate
2. Weight accurately 5 g of product in the plate
3. Dry at 40°C under vacuum for 4 hours, until constant weight

Before weighing, let the product cool to room temperature into a desiccator.

Calculations

Product weight = Gross weight (before drying) – Plate tare weight
Lost weight = Gross weight (before drying) – Goss weight (after drying)

$$\text{Loss on Drying \%} = \frac{\text{Lost Weight} \times 100}{\text{Product weight}}$$

CHLORIDES

Chlorides	NMT 100 ppm (0.01%)	8.0601

Method: USP <221> Modified

Reagents	Preparation
Sodium Chloride (pure reagent)	
Water (Deionized)	
Nitric Acid 2 N	
Silver Nitrate Solution	Dissolve 1.7 g in 100 mL of water

Test solution (0.033 g/mL)

Dissolve 0.5 g of product in 15 mL of water

Stock Standard solution (5 ppm)

1. Dissolve exactly 824 mg of NaCl in 1 L of water
2. Take 1 mL and dilute to 100 mL with water

NB: this solution can be stored and used many times.

Standard Solution (50 µg – corresponding to 100 ppm in the test solution)

- Take 10 mL of the Stock Standard Solution and add 5 mL of water

Procedure

Using the Test and Standard Solution, perform the following test.

1. Add 1 mL of Nitric Acid 2 N, mix well
2. Add the solution into a test tube containing 1 mL of Silver Nitrate Solution
3. Protect from light and wait 5 minutes
4. Observe the opalescence against a black background

The Test Solution should show less turbidity than the Standard Solution.

ASSAY BY TITRATION

Assay by titration	97.0 – 102.0% (on dried basis)	9.0601

Equipment

- Titroprocessor Metrohm 751 or similar
- Dosimat Metrohm 685 or similar
- Balance Mettler Toledo AG 245 or similar

Solent: Water/Sulfuric Acid

Potassium Iodate 0.1 N (Titrating agent): Dissolve 3.567 g of potassium iodate, previously dried at 110° to constant weight, in water and bring to 1000 mL.

Sulfuric acid 3.6 N: Carefully and with constant cooling, dilute 19 mL of 98% Sulfuric acid to 100 mL of water.

Procedure

1. Dissolve about 0.350 g of sample in 100 mL of water
2. Add 10 mL of 3.6 N Sulfuric Acid
3. Add 1.0g of Potassium Iodide and 2 mL of fresh starch indicator
4. Titrate with Potassium Iodate 0.1 N to a pale blue end point, persisting for more than 30 seconds

5. Perform a blank determination and make any necessary correction

Calculations

$$\textit{Assay (Iodate, as is) \%} = \frac{\textit{mL Iodate x factor x 2.272}}{\textit{Weight (g)}}$$

The assay must be calculated on dried substance with the formula:

$$\textit{Assay (Iodate, ODB) \%} = \frac{\textit{Assay\%}}{\textit{100 - LOD}} \textit{ x 100}$$

LOD is the Loss on drying.

Remark: The Assay (Iodate, as is) is used also for the calculations reported in the following tests.

- *test n°10 (Free tartaric acid)*
- *test n°11 (Cystamine content)*

FREE TARTARIC ACID

Free Tartaric Acid	NMT 1.0%	10.0601

Equipment

- Titroprocessor Metrohm 751 or similar
- Dosimat Metrohm 685 or similar
- Balance Mettler Toledo AG 245 or similar

Solvent: Water

Titrating agent: Sodium hydroxide 0.1 N (NaOH)

Procedure

1. Dissolve about 0.350 g of sample in 100 mL of water
2. Titrate with NaOH 0.1 N, determining the end point potentiometrically
3. Perform a blank determination and make any necessary correction

Calculations

$$\textit{Assay (NaOH) \%} = \frac{\textit{mL NaOH x factor x 2.272}}{\textit{Weight (g)}} \textit{ (usually between 98\% - 101\%)}$$

$$\textit{Free Tartaric acid \%} = \frac{\textit{Assay (NaOH) – Assay (Iodate, as is)}}{2}$$

Remark: if Assay (Iodate, as is) is higher than the Assay (NaOH), free cysteamine is present.

CYSTAMINE CONTENT

Cystamine content	NMT 2.0%	11.0701

Equipment

- Titroprocessor Metrohm 751 or similar
- Dosimat Metrohm 685 or similar
- Balance Mettler Toledo AG 245 or similar

Solent: Acetic Acid

Titrating agent: Perchloric Acid 0.1 N ($HClO_4$)

Procedure

1. Dissolve about 0.300 g of sample in 80 mL Acetic acid
2. Titrate with perchloric acid, determining the end point potentiometrically
3. Perform a blank determination and make any necessary correction

Calculations

$$Assay\ (HClO_4)\ \% = \frac{mL\ HClO_4 \times factor \times 2.272}{Weight\ (g)}$$

Cystamine % = Assay ($HClO_4$) - Assay (Iodate, as is)

PARTICLE SIZE

Particle Size	NLT 50% < 150 microns NLT 90% < 450 microns	12.0601

Equipment

- Microscope Leitz SM-LUX

Procedure

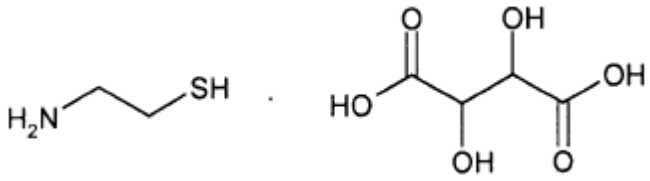
1. Distribute the powder on a glass-plate, using paraffin oil
2. Verify that the granulometric distribution is homogeneous
3. Evaluate the dimension of the particles using the graduated scale

At least 50% of the particles must be lower than 150 microns

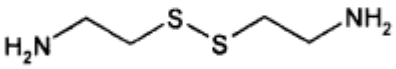
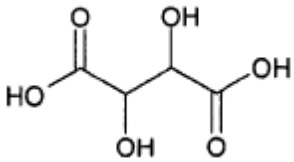
At least 90% of the particles must be lower than 450 microns

CYSTEAMINE BITARTRATE

(Mercaptoethyl) ammonium hydrogen tartrate



RELATED SUBSTANCES

Cystamine	
Tartaric Acid	

2.1.S.4.3 Validation of analytical procedures

The titration methods for:

- ASSAY – Titration with Potassium Iodate
- FREE TARTARIC ACID – Titration with NaOH and Potassium Iodate
- CYSTAMINE - Titration with HClO4 and Potassium Iodate

have been developed in-house at Cambrex Profarmaco Milano S.r.l. and validated.

All these methods are routinely used on all batches. A summary of the available validation results using a sample of cysteamine bitartrate coming from the standard production (Lot# 460202) is reported below. All the acceptance criteria have been met.

Analyte/Method	**Range**	**Linearity Correlation coefficient**	**Precision (%RSD)**
Cysteamine bitartrate -Titrate with 0.1 N potassium iodate	80-120%	1.000	0.06%
Free tartaric acid -Titration with 0.1 N NaOH	80-120%	1.000	0.07 %
Cystamine - Titration with $HClO_4$	80-120%	1.000	0.07 %

*RSD: Relative Standard Deviation

2.1.S.4.4 Batch analyses

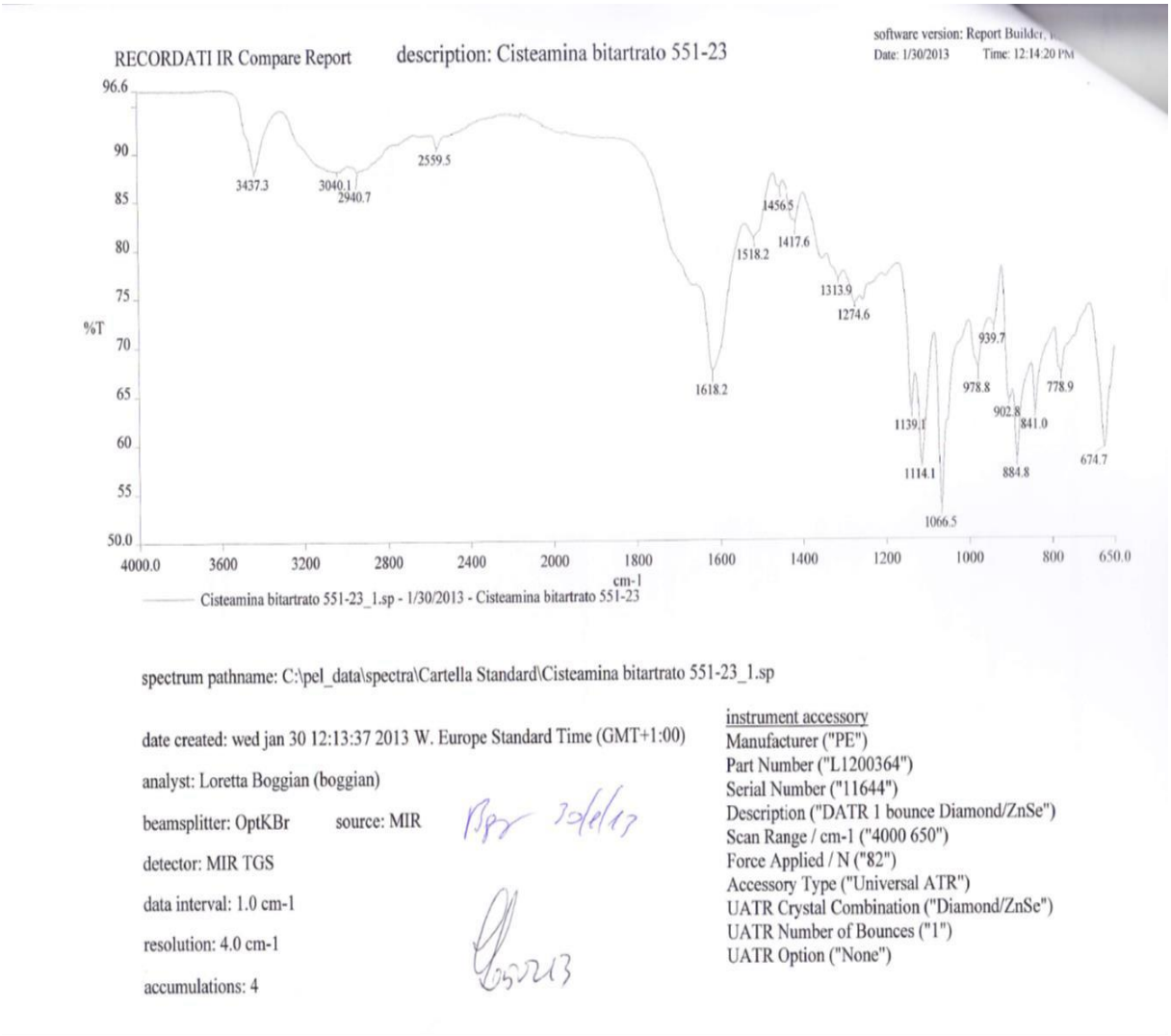
The analytical results of the recent standard production batches of cysteamine bitartrate from Cambrex Profarmaco Milano are reported in the **Section 2.1.S.5**. The results enclosed show that cysteamine bitartrate complies with the specifications for the final product.

2.1.S.4.5 Justification of specification(s)

The active ingredient cysteamine bitartrate is not described in any official Pharmacopoeia. All the tests included in the specification for the final product have been internally developed by Cambrex Profarmaco Milano. Further information on the justifications of specifications would be provided to the assessor directly by Cambrex Profarmaco Milano S.r.l. as and when required by the authorities.

2.1.S.5 Reference standards or materials

Reference FTIR Spectra for cysteamine API is provided below.



A copy of the certificate of analysis for the working standard is provided below and the characterization and spectrum are reported in **Section 2.1.2.3 Characterization**. The standard batch size for cysteamine bitartrate manufactured by Cambrex Profarmaco Milano is about 140 Kg (± 15%) (*).

Cysteamine bitartrate					
Lot number	822324	822526	822728	860202	880304
Manufacturing date	Jun 2019	Jun 2019	Jun 2019	June 2020	Mar 2021
Re-analysis date	Feb 2020	Mar 2020	Mar 2020	Mar 2021	Dec 2021
Batch size	276 Kg	259 Kg	279 Kg	145 Kg	292.8 Kg

(*) According to Cambrex Profarmaco Milano internal SOP a maximum scale factor of 3 can be applied.

Cysteamine bitartrate API from the **lot number # 860202** was used in the manufacturing of the IMP, IV cysteamine bitartrate for use in the REMAP-CAP trial. API from **lot number #880304** was used as a reference standard for IMP batch release. References standard from the fresh batch of API will be purchased whenever required for testing or release.

CoA of the reference standard of cysteamine bitartrate Batch No. 822324.

Cambrex

Cambrex Profarmaco Milano S.r.L.

Via Curiel 34, 20067 Paullo (MI) - ITALY Tel.: +39 02 90 62 60.1

Certificate of Analysis

Product	**CYSTEAMINE BITARTRATE (M)**	C.A.S. n.	27761-19-9
Batch	**822324**	Formula	C2H7NS(C4H6O6)
Production date	**June 2019**	M.W.	227.2
Re-Analysis Date	**February 2020**	T.S.	010.004
Analysis	**June 19 2019**	Coa issued on	October 25 2019
Coa Number	**CA9.938**		

DETERMINATION	SPECIFICATION		RESULT
DESCRIPTION	White crystalline powder		COMPLIES
SOLUBILITY	Water	Clear solution	COMPLIES
COLOUR	Abs at 420 nm in water	NMT 0.100	0.008
IDENTIFICATION	IR spectrum Melting Range	Conforms to standard 118 / 121 °C	COMPLIES 119
RESIDUE ON IGNITION		NMT 0.1 %	0.0
LOSS ON DRYING		NMT 0.5 %	0.1
CHLORIDES		NMT 100 ppm	COMPLIES
ASSAY	By titration (on dried basis)	97.0 / 102.0 %	98.8
FREE TARTARIC ACID		NMT 1.0 %	0.0
CYSTAMINE CONTENT		NMT 2.0 %	1.1
PARTICLE SIZE	< 150 microns < 450 microns	NLT 50% NLT 90%	COMPLIES COMPLIES

This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7)

Storage conditions: Triplex aluminium, not under vacuum-packed, 5 +/- 3 °C

Approved by Qualified Person / Quality Director
Laura Bigini
10-25-2019 10:43

This Certificate of Analysis has been approved by the Qualified Person / Quality Director and produced automatically with validated electronic signature

Page 1 of 1

CoA of the reference standard of cysteamine bitartrate Batch No. 822526.

Cambrex

Cambrex Profarmaco Milano S.r.L.

Via Curiel 34, 20067 Paullo (MI) - ITALY Tel.: +39 02 90 62 60.1

Certificate of Analysis

Product	**CYSTEAMINE BITARTRATE (M)**	C.A.S. n.	27761-19-9
Batch	**822526**	Formula	C2H7NS(C4H6O6)
Production date	**June 2019**	M.W.	227.2
Re-Analysis Date	**March 2020**	T.S.	010.004
Analysis	**June 19 2019**	Coa issued on	October 25 2019
Coa Number	**CA9.939**		

DETERMINATION	SPECIFICATION		RESULT
DESCRIPTION	White crystalline powder		COMPLIES
SOLUBILITY	Water	Clear solution	COMPLIES
COLOUR	Abs at 420 nm in water	NMT 0.100	0.004
IDENTIFICATION	IR spectrum Melting Range	Conforms to standard 118 / 121 °C	COMPLIES 120
RESIDUE ON IGNITION		NMT 0.1 %	0.0
LOSS ON DRYING		NMT 0.5 %	0.1
CHLORIDES		NMT 100 ppm	COMPLIES
ASSAY	By titration (on dried basis)	97.0 / 102.0 %	99.5
FREE TARTARIC ACID		NMT 1.0 %	0.0
CYSTAMINE CONTENT		NMT 2.0 %	0.6
PARTICLE SIZE	< 150 microns < 450 microns	NLT 50% NLT 90%	COMPLIES COMPLIES

This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7)

Storage conditions: Triplex aluminium, not under vacuum-packed, 5 +/- 3 °C

Approved by Qualified Person / Quality Director
Laura Bigini
10-25-2019 10:44

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CoA of the reference standard of cysteamine bitartrate Batch No. 822728.

Cambrex

Cambrex Profarmaco Milano S.r.L.

Via Curiel 34, 20067 Paullo (MI) - ITALY Tel.: +39 02 90 62 60.1

Certificate of Analysis

Product	**CYSTEAMINE BITARTRATE (M)**	C.A.S. n.	27761-19-9
Batch	**822728**	Formula	C2H7NS(C4H6O6)
Production date	**June 2019**	M.W.	227.2
Re-Analysis Date	**March 2020**	T.S.	010.004
Analysis	**June 25 2019**	Coa issued on	October 25 2019
Coa Number	**CA9.940**		

DETERMINATION	SPECIFICATION		RESULT
DESCRIPTION	White crystalline powder		COMPLIES
SOLUBILITY	Water	Clear solution	COMPLIES
COLOUR	Abs at 420 nm in water	NMT 0.100	0.003
IDENTIFICATION	IR spectrum Melting Range	Conforms to standard 118 / 121 °C	COMPLIES 120
RESIDUE ON IGNITION		NMT 0.1 %	0.0
LOSS ON DRYING		NMT 0.5 %	0.1
CHLORIDES		NMT 100 ppm	COMPLIES
ASSAY	By titration (on dried basis)	97.0 / 102.0 %	98.7
FREE TARTARIC ACID		NMT 1.0 %	0.0
CYSTAMINE CONTENT		NMT 2.0 %	1.4
PARTICLE SIZE	< 150 microns < 450 microns	NLT 50% NLT 90%	COMPLIES COMPLIES

This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7)

Storage conditions: Triplex aluminium, not under vacuum-packed, 5 +/- 3 °C

Approved by Qualified Person / Quality Director
Laura Bigini
10-25-2019 10:44

This Certificate of Analysis has been approved by the Qualified Person / Quality Director and produced automatically with validated electronic signature

Page 1 of 1

CoA of the reference standard of cysteamine bitartrate Batch No. 860202.

Cambrex Profarmaco Milano S.r.L.

Via Curiel 34, 20067 Paullo (MI) - ITALY Tel.: +39 02 90 62 60.1

Certificate of Analysis

Product	**CYSTEAMINE BITARTRATE (M)**	C.A.S. n.	27761-19-9
Batch	**860202**	Formula	C2H7NS(C4H6O6)
Production date	**June 2020**	M.W.	227.2
Re-Analysis Date	**March 2021**	T.S.	010.004
Analysis	**July 7 2020**	Coa issued on	November 26 2020
Coa Number	**CA12.846**		

DETERMINATION	SPECIFICATION		RESULT
DESCRIPTION	White crystalline powder		**COMPLIES**
SOLUBILITY	Water	Clear solution	**COMPLIES**
COLOUR	Abs at 420 nm in water	NMT 0.100	**0.002**
IDENTIFICATION	IR spectrum Melting Range	Conforms to standard 118 / 121 °C	**COMPLIES** **118**
RESIDUE ON IGNITION		NMT 0.1 %	**0.0**
LOSS ON DRYING		NMT 0.5 %	**0.1**
CHLORIDES		NMT 100 ppm	**COMPLIES**
ASSAY	By titration (on dried basis)	97.0 / 102.0 %	**98.0**
FREE TARTARIC ACID		NMT 1.0 %	**0.3**
CYSTAMINE CONTENT		NMT 2.0 %	**1.4**
PARTICLE SIZE	< 150 microns < 450 microns	NLT 50% NLT 90%	**COMPLIES** **COMPLIES**

This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7)

Storage conditions: Triplex aluminium, not under vacuum-packed, 5 +/- 3 °C

Approved by Qualified Person / Quality Director

Laura

CoA of the reference standard of cysteamine bitartrate Batch No. 880304

Cambrex

Cambrex Profarmaco Milano S.r.l.

Via Curiel 34, 20067 Paullo (MI) - ITALY Tel.: +39 02 90 62 60.1

Certificate of Analysis

Product	CYSTEAMINE BITARTRATE (H)	C.A.S. n.	27761-19-9
Batch	880304	Formula	C2H7NS(C4H6O6)
Production date	March 2021	M.W.	227.2
Re-Analysis Date	December 2021	T.S.	010.004
Analysis	March 18 2021		
Coa Number	CA13.513		

DETERMINATION	SPECIFICATION		RESULT
DESCRIPTION	White crystalline powder		COMPLIES
SOLUBILITY	Water	Clear solution	COMPLIES
COLOUR	Abs at 420 nm in water	NMT 0.100	0.001
IDENTIFICATION	IR spectrum	Conforms to standard	COMPLIES
	Melting Range	118 / 121 °C	120
RESIDUE ON IGNITION		NMT 0.1 %	0.0
LOSS ON DRYING		NMT 0.5 %	0.0
CHLORIDES		NMT 100 ppm	COMPLIES
ASSAY	By titration (on dried basis)	97.0 / 102.0 %	99.9
FREE TARTARIC ACID		NMT 1.0 %	0.0
CYSTAMINE CONTENT		NMT 2.0 %	0.4
PARTICLE SIZE	< 150 microns	NLT 50%	COMPLIES
	< 450 microns	NLT 90%	COMPLIES

This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7)

Storage conditions: Triplex aluminium, not under vacuum-packed, 5 +/- 3 °C

Approved by Qualified Person / Quality Director
Laura Bigini
03-19-2021 12:41

This Certificate of Analysis has been approved by the Qualified Person / Quality Director and produced automatically with validated electronic signature

Page 1 of 1

2.1.S.6 Container closure system

The commercial packaging system for cysteamine bitartrate composed of aluminium bags, plastic drums and closure systems is fully described in this section. The specifications of the suppliers, reporting the general characteristics of drums and bags and certifying their food-grade are enclosed.

Cysteamine bitartrate is packed into LDPE polyethylene coated aluminium bag, heat sealed but not under vacuum. Aluminium bags are packed inside a polyethylene bag and then into plastic drums. The material must be stored in refrigerated conditions (2-8°C), according to label reported in the following section.

The top lid of the drum is sealed with an aluminium seal with our trademark, not removable without breaking. We use plastic drums of different capacities, as reported in the following table:

Capacity	**U.M.**
6 (*)	litres
8	litres
17(*)	litres
28	litres
50	litres
60	litres
110	litres
125	litres
150	litres

The drums and bags are stored in a proper room protected from contamination. Every plastic drum and bag is checked for cleanliness by the operator before use. The drums, containing the final API and coming from the finishing department, are weighed in a proper room protected from contamination, opened for visual inspection and the labels are replaced with the official ones (one internal on the polyethylene bag and one external on the drum's body).

ALUMINUM BAGS

Characteristics:

The aluminium bags have different sizes.

They are heat sealed with a special machine and then put inside plastic drums.

POLYETHYLENE BAGS

Characteristics:

The bags used are made of polyethylene of low density (LDPE) and are food-grade.

PLASTIC DRUMS

Characteristics:

Body	HDPE HMW
Lid	HDPE
Gasket	Natural gum / Polyurethanic bi-component gum
Closure ring	in zinc steel, with sealing lever

(*) The plastic drums of 6 and 17 litres are closed with a screw top lid and sealed with a plastic lace with our trademark non removable without tampering.

CLOSURE SYSTEMS

Characteristics:

Each aluminium bag is heat sealed and put into plastic drums.

The top lid for plastic drums is sealed with an aluminium seal with our trademark in order to avoid tampering.

SPECIFICATIONS

The specifications of the suppliers, the commercial packaging system, reporting the general characteristics of drums and bags, analytical specifications of the bags (aluminium and polyethylene bags) and certifying their food-grade are enclosed in the following pages.

Aluminium bag – Analytical specifications

CAMBREX

Cambrex Profarmaco Milano S.r.l.

Formula	MW	Product Code	Date	Edition
		S26	09/2015	001.001

TRIPLEX (PET/ALU/PE) BAG 55X100

Approved by QA	Approved by QC	
		RAW MATERIALS

WEIGHT	**11-13 g (10 x 10 cm)**

Weight a sample with a size of 10 x 10 cm.
The weight must in the range 11-13 g.

RESIDUAL SOLVENT (BY HS/GC)

NAME	HIGHT LIMIT
Any single peak	150 mV

COLUMN	CARRIER	FLOW
OVI-G43, 30 m, 0.53mm x 3µ Transfer line: Fused Silica 1.2 M x 0.32mm Back Column: Deact. Column Int. Polarity 5 m x 0.25 mm	Nitrogen	17 psi

DETECTOR	300°	**HS TEMP.**	50°	**EQ.TIME**	20 min	**WDR TIME**	0.2 min
INJECTOR	NA	**NEDDLE**	200°	**PRES.TIME**	3 min	**VENT TIME**	0.1 min
INJ.VOL.	500 µL	**TR.LINE**	200°	**VIAL VOL.**	22 ml	**RUN TIME**	10

OVEN	200°x10'	**REMARKS**	Att. 1

SAMPLE PREPARATION	1 PIECES 5X17 cm

Prepare a sample for each bag that has been sampled (three bag for each bad taken from three different boxes).

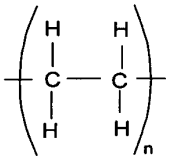
S26 TS 001.001 Pagina 1 di 1

Polyethylene bag – Analytical specifications

CAMBREX

Cambrex Profarmaco Milano S.r.l.

Formula	MW	Product Code	Date	Edition
$(C_2H_4)_n$	28.054	**S12**	11/2014	001.001
POLYETHYLENE BAG 50X60				
Approved by QA	Approved by QC			
		RAW MATERIALS		



IDENTIFICATION	IR spectrum

IR spectrum of the sample is the same as the reference (see the attached IR spectrum).

RESIDUAL SOLVENT (BY HS/GC)

NAME	HIGHT LIMIT
Any single peak	150 mV

COLUMN	CARRIER	FLOW
OVI-G43, 30 m, 0.53mm x 3µ Transfer line: Fused Silica 1.2 M x 0.32mm Back Column: Deact. Column Int. Polarity 5 m x 0.25 mm	Nitrogen	17 psi

DETECTOR	300°	HS TEMP.	50°	EQ.TIME	20 min	WDR TIME	0.2 min
INJECTOR	NA	NEDDLE	200°	PRES.TIME	3 min	VENT TIME	0.1 min
INJ.VOL.	500 µL	TR.LINE	200°	VIAL VOL.	22 ml	RUN TIME	10

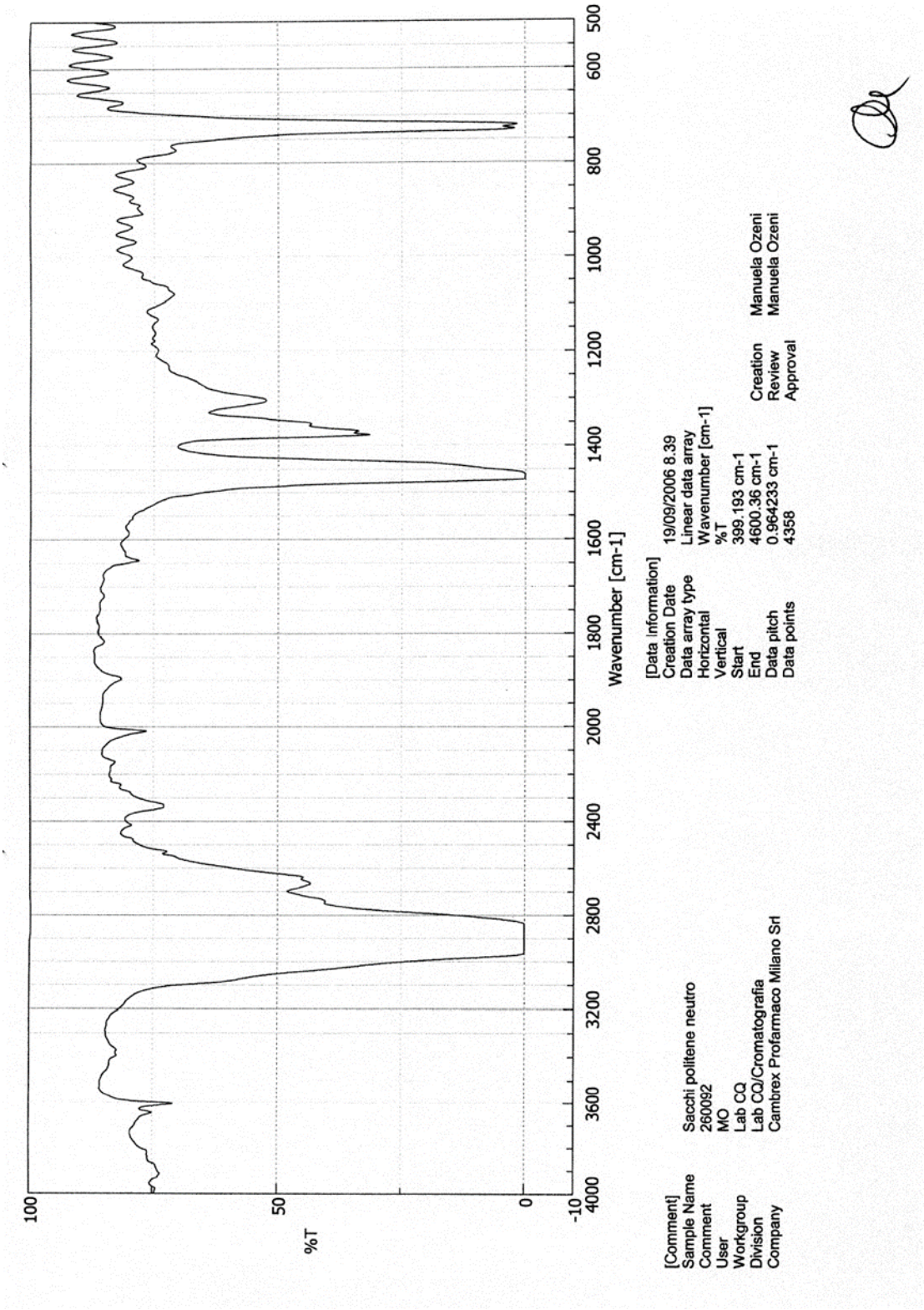
OVEN	200°x10'	REMARKS	Att. 1

SAMPLE PREPARATION	2 PIECES 5X17 cm

Prepare a sample for each bag that has been sampled (three bag for each bad taken from three different boxes).

S12 TS 001.001 Pagina 1 di 1

IR Polyethylene bag



Aluminium bags

Cel Vil
di Maurizio & Andrea Villa s.n.c.

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C.C.I.A.A. MILANO 1194546 - C.F. e P.I. 08015130159

FILM FLESSIBILI PER IMBALLAGGI - BUSTE - SACCHETTI
STAMPA FLESSOGRAFICA
CELLOPHANE - POLIPROPILENE - POLIETILENE LD/HD
PVC - ACCOPPIATI PER ALIMENTI

TECHNICAL DATA SHEET

PRODUCT CODE	NPETALUPE140		
DESCRIPTION	NEUTRAL FILM		
STRUCTURE	PET/ALU/PE		
ADHESIVE	SOLVENTLESS	DATE	29/10/2015

MAIN PHYSICAL CHARACTERISTICS

USE	1-2-4	1-PACKAGING 2-PASTEURIZABLE 3-STERILIZABLE 4-FOOD 5-NO FOOD	
WIDTH	-	CORE DIAMETER	76 mm
TOLERANCE	+/- 2 mm		

	THICKNESS (µm)	WEIGHT (g/m²)	DENSITY (Kg/dm³)
PET	12	17,1	1,14
ADHESIVE	-	2	1,16
ALUMINIUM	8	22	2,75
ADHESIVE	-	2	1,16
POLYETHYLENE	120	67,5	0,9
TOTAL	140	110,60	-

	UNIT	VALUE	METHOD
YIELD	m²/Kg	9	INTERNAL
COF (max)	-	0,2	ASTM D 1894

SEALABLE LAYER

	UNIT	VALUE	METHOD
INITIAL TENPERATURE SEALING	°C	110°	INTERNAL

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FILM FLESSIBILI PER IMBALLAGGI - BUSTE - SACCHETTI
STAMPA FLESSOGRAFICA
CELLOPHANE - POLIPROPILENE - POLIETILENE LD/HD
PVC - ACCOPPIATI PER ALIMENTI

DICHIARAZIONE DI CONFORMITA' DEI MATERIALI E DEGLI OGGETTI DESTINATI A VENIRE A CONTATTO CON PRODOTTI ALIMENTARI

Con la presente si dichiara che il materiale **NPETALUPE140** fornitoVi

è conforme

alla seguente legislazione comunitaria CE:

- **Regolamento 1935/2004/CE**
- **Regolamento 1895/2005/CE**
- **Regolamento 10/2011/CE**
- **Direttiva 2002/72/CE** e successivi aggiornamenti e modifiche
- **Direttiva 94/62/CE** riguardante i limiti di concentrazione di piombo, mercurio, cadmio e cromo esavalente
- **Direttiva 85/572, 82/711, 93/48, 97/48**

ed alla seguente legislazione italiana:

- **Decreto Ministeriale 21/03/1973** e successivi aggiornamenti e modifiche
- **DPR 777/82** e successivi aggiornamenti e modifiche

In accordo con il **Regolamento 2023/2006/CE** il seguente film viene lavorato nel rispetto delle norme generali sulle buone pratiche di fabbricazione (**GMP**).

Il materiale sopracitato è costituito da:

- PET (polietilene tereftalato)
- Adesivo (poliuretanico bicomponente senza solvente)
- ALLUMINIO
- Adesivo (poliuretanico bicomponente senza solvente)
- POLIETILENE **(lato che entra in contatto con il prodotto alimentare)**

Cel Vil
di Maurizio & Andrea Villa s.n.c.

FILM FLESSIBILI PER IMBALLAGGI - BUSTE - SACCHETTI
STAMPA FLESSOGRAFICA
CELLOPHANE - POLIPROPILENE - POLIETILENE LD/HD
PVC - ACCOPPIATI PER ALIMENTI

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C.C.I.A.A. MILANO 1194546 - C.F. e P.I. 08015130159

Dai dati forniti dai produttori di materia prima si dichiara che il materiale contiene sostanze sottoposte a restrizioni nelle legislazioni citate. Il materiale rispetta i limiti di migrazione globale e le restrizioni specifiche nelle seguenti condizioni di prova:

Simulante	Descrizione	Metodo	Unità di Misura	Valore test	
Simulante A	Etanolo 10%	D.M. 21/03/1973 GRAVIMETRICO	mg/dm^2	<1	
Simulante B	Acido acetico 3%	D.M. 21/03/1973 GRAVIMETRICO	mg/dm^2	1,2	
Simulante D2	Olio d'oliva rettificato	D.M. 21/03/1973 GRAVIMETRICO	mg/dm^2	<1	

Il limite di migrazione globale, unitamente alle altre restrizioni specifiche alle quali possono essere sottoposti i monomeri e/o gli additivi presenti nel materiale, sono rispettati nelle condizioni d'uso sopra menzionate.
L'affermazione è supportata da prove analitiche oppure in base a calcoli sulla migrazione delle sostanze condotti in accordo con le direttive 82/711/CEE, 85/572/CEE e 97/48/CE e DM 21 marzo 1973, ove applicabili. I calcoli sono stati effettuati assumendo che 1 kg di alimento venga in contatto con 6 dm^2 di prodotto.

Dalle informazioni ricevute dai produttori delle materie prime, si dichiara la totale assenza di additivi denominati dual use.

Specifiche d'uso:
il materiale in oggetto è destinato a venire a contatto (lato polietilene) con:

- Paste secche e fresche, biscotti e prodotti da forno, pasticceria, caffè, latticini freschi e stagionati, verdure, ortaggi, surgelati, salumi e carni.

Sono assenti allergeni alimentari di cui alla direttiva 2007/68/EC allegato III.

Questa dichiarazione è redatta in conformità alla legislazione sopra citata ed è destinata a: CAMBREX PROFARMACO MILANO SPA

Questa dichiarazione ha validità a partire dalla data sotto riportata e sarà sostituita nel caso in cui interverranno cambiamenti sostanziali nella produzione e lavorazione del materiale in grado di mutare alcuni requisiti essenziali ai fini della conformità o quando i riferimenti legislativi citati nella presente dichiarazione saranno modificati e aggiornati in modo da richiedere una nuova verifica ai fini della conformità.
La dichiarazione ha comunque una validità temporale massima di 24 mesi.

Data, 03.03.2014

CEL VIL
di Maurizio & Andrea Villa Snc
Via De Ruggero, 15
20019 - SETTIMO MILANESE (MI)
Tel. 02 33501188 - Fax 02 33500711
P.I. e C.F. 08015130159

03/03/2014

DECLARATION OF CONFORMITY
(English version of "DICHIARAZIONE DI CONFORMITA'")

We herewith confirm that the material PET/ALU/PE140 we supply you is in compliance with the following Community legislation CE:

Regulations 1935/2004/CE
Regulations 1895/2005/CE
Regulations 10/2011/CE
Directive 2002/72/CE and following updates and modifications
Directive 94/62/CE on the limits for Pb, Hg, Cd, Cr (VI)
Directive 85/572, 82/711, 93/48, 97/48

and the following Italian legislation:
DM 21/03/73 and following updating and modifications
DPR 777/82 and following updating and modifications

According to Regulation 2023/2006/CE this film is manufactured according to Good Manufacturing Practices (GMP)

The above product is manufactured with the following materials:

PET
Adhesive (bicomponent Polyurethanic without solvent)
Aluminium
Adhesive (bicomponent Polyurethanic without solvent)
Polyethylene (in contact with the food stuff)

The material contains substances which are subject to restrictions in the mentioned laws. The material complies with the limit of overall migration and the specific restrictions in the following test conditions:

Simulant: A (Ethanol 10%)	< 1 mg/dm2	(DM 21/03/1973 Gravimetric)
Simulant: B (Acetic acid 3%)	1.2 mg/dm2	(DM 21/03/1973 Gravimetric)
Simulant: D2 (Olive oil)	< 1 mg/dm2	(DM 21/03/1973 Gravimetric)

The limit of overall migration together with the other specific restrictions which the monomers and/or additives of the material can be subject to are satisfied in the above mentioned use conditions. This is supported by analytical tests performed in compliance with Directives 82/711/CE, 85/572/CE and 97/48/CE and DM 21/03/73. The calculations have been carried out assuming that 1 kg of food comes in contact with 6 dm^2 of packaging material.
We can declare that dual use additives are totally absent.

The material can come into contact with:
Pasta, biscuits and oven products, patisserie, coffee, milk and derivatives, vegetables, frozen products, meat.
Alimentary allergens according to Directive 2007/68/EC Attachment III are absent.

This declaration is valid starting from the above indicated date and will be replaced when important changes occur in the production of material so as to modify some essential requirements in terms of conformity or when the legislative references indicated are modified and updated so that a revision will be necessary in order to comply with them. This declaration is in any case valid for 24 months.

Cel Vil
di Maurizio & Andrea Villa s.n.c.
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VIA DE RUGGERO, 15
Tel. +39 02 33501188 r.a. - Fax +39 02 33500711
e.mail: info@celvil.it - http: //www.celvil.it
C.C.I.A.A. MILANO 1194546 - C.F. e P.I. 08015130159

FILM FLESSIBILI PER IMBALLAGGI - BUSTE - SACCHETTI
STAMPA FLESSOGRAFICA
CELLOPHANE - POLIPROPILENE - POLIETILENE LD/HD
PVC - ACCOPPIATI PER ALIMENTI

SPETT.LE
CAMBREX PROFARMACO MILANO SRL
VIA CUCCHIARI 17
20155 MILANO

SETTIMO MILANESE, 01 Luglio 2011

OGGETTO: DICHIARAZIONE DI IDONEITA' ALIMENTARE PER IL PRODOTTO POLIETILENE

Con la presente si dichiara che i prodotti in oggetto sono idonei al contatto con sostanze alimentari come previsto dall'Art. 5 del D.M. del ministero della sanità del 21.03.1973 e i successivi aggiornamenti ed in recepimento delle direttive CEE corrispondenti.

I prodotti in oggetto hanno superato le prove per tutti e quattro i simulanti alimentari previsti dal D.M. 220 del 26.04.1993 e sono quindi adatti per venire a contatto con tutti gli alimenti come descritto nella tabella del Decreto stesso.

I monomeri e le altre sostanze usate per la produzione dei film sono incluse nella direttiva CEE 90/128 del 23.02.90 e successivi aggiornamenti.

Tale idoneità al contatto con gli alimenti va intesa per il materiale pulito.

Si dichiara inoltre che i prodotti sono conformi in base al regolamento (CE) N.2023/2006 della commissione del 22 dicembre 2006 sulle buone pratiche della fabbricazione dei materiali e degli oggetti destinati a venire a contatto con prodotti alimentari.

La Cel Vil è ha disposizione per fornire a chi ne facesse specifica richiesta, copia dell'analisi chimica sui materiali.

CELVIL SNC

July 1st, 2011

DECLARATION OF POLIETHYLENE SUITABILITY FOR FOODSTUFFS
(English version of "DICHIARAZIONE DI IDONEITA' ALIMENTARE")

We declare herewith that the above product is suitable for coming in contact with foodstuffs as required by Art. 5 D.M. Ministero della Sanità dated 21/03/1973 and following updating and according to relevant CEE directives.

The above product has passed the test for all the four food simulants indicated in D.M. 220 dated 26/04/1993 and is suitable for coming in contact with all kinds of food as described in the table included in the Decree itself.

Monomers and the other substances used to produce the films are included in CEE Directive 90/128 dated 23/02/90 and following updating.

The suitability for foodstuffs is to be intended for clean materials.

We also declare that the products comply with CE regulations N. 2023/2006 dated 22/12/2006 on the good manufacture practices of the materials intended to come in contact with foodstuffs.

A copy of the chemical analysis of the materials can be provided by Celvil on request.

dioki

DiOKI d.d.
10000 Zagreb, Žitnjak, Croatia

[redacted]

The name of the product: **Okiten 245 A/S**

Company: DiOKI d.d. Organic petrochemistry
Žitnjak bb, 10000 Zagreb, Croatia
Phone: +385 1 2483000
Fax: +385 1 2404 151

Emergency phone: **+385 1 2483000/3111**

[redacted]

Chemical characterization /group: Polyethylene

Hazardous ingredients: None

[redacted]

Risk identification for human health and environment: None

[redacted]

First aid - inhalation:
First aid - skin contact: Wash off thoroughly with water and soap. Burns caused by the melted material should be treated /by a doctor/ at a clinic.
First aid - eye contact: Rinse thoroughly with running water for 15 minutes.
First aid - ingestion: No special measures required.

[redacted]

Extinguishing media: Water, foam, carbon dioxide (CO_2), and dry extinguishing media.
Dangerous combustion products are carbon monoxide and dioxide (CO, CO_2).
Special protective equipment:

R-03-1-09.2e "3"

[redacted]

Personal protection: No special measures
Environmental protection: No special measures.
Methods for cleaning up and removal: Sweep up for risk of slipping.

[redacted]

Handling: with air conveying system refer to Guideline for technical standard dealing with/concerning protection against static electricity build-up (Croatian Official Gazette 62/73).

Fire and explosion protection:
Prevent accumulation of PE particles (< 0.125 mm), especially with air conveying system.
As the product contains flammable polymers, appropriate fire protection measures should be taken.

[redacted]

Precautionary measures in working area: Refer to Section 7.
Engineering measures: Good general ventilation should be sufficient. Local exhaust ventilation may be necessary for some operations.
Avoid inhalation of gaseous products of material decomposition.

[redacted]

Shape:	granules
Colour:	natural (noncolored)
Odour:	odourless
Change of state:	
Melting point/melting range:	114 °C (DSC)
Explosion limits:	
upper:	20 g/m³
lower:	about 2000 g/m³
Ignition point:	>340 °C
Density: (23 °C)	0,924 g/cm ³ (ISO 1183)
Bulk density:	560 kg/m³
Water solubility:	insoluble

[redacted]

R-03-1-09.2e "3"

Thermal degradation: > 350 °C (DSC)
Inflammable gases and vapours are generated.

Dangerous reactions to avoid:
Hazardous dust explosion, particle accumulation (dust), especially with air conveying system.

Hazardous products of decomposition:Monomer, inflammable gases and vapours

[redacted]

In normal use and handling the product has no harmful effect to health.

[redacted]

Biologically not degradable.
Recycling possible.

[redacted]

Local regulations should be observed.

Contaminated packaging should be cleaned prior to recycling.

[redacted]

Not classified as dangerous material according to transport regulations (Croatian law on transportation of dangerous materials - NN 97/93).

[redacted]

Labelling is not the subject of EEC Directives.

[redacted]

R-03-1-09.2e "3"

polimeri europa
Direzione e Uffici Amministrativi
Piazza Boldrini, 1 - 20097 San Donato Milanese (MI)
tel. centralino +39 02 5201
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DICHIARAZIONE DI CONFORMITA' ALLA FARMACOPEA

RIBLENE FF 22, FF 33, FF 34, FL 23, FL 30 (produced in Italy), FL 34 E, FM 34E, FM 53, MP 30 (produced in France), MP 31, MP 31 R, FL 34D.

I prodotti, così come da noi forniti in imballi originali, sono conformi per composizione a quanto prescritto dalle monografie della Farmacopea relative alle poliolefine per uso medico-farmaceutico:

- EUROPEAN PHARMACOPOEIA
  - 3.1.3 "POLYOLEFINES" (7th EDITION – 2011).
  - 3.1.5 "POLYETHYLENE WITH ADDITIVES FOR CONTAINERS FOR PREPARATIONS FOR PARENTERAL USE AND FOR OPHTHALMIC PREPARATIONS" (7th EDITION – 2011).
- USA — USP 34 "POLYETHYLENE CONTAINERS"

Nella preparazione dei prodotti sopraindicati non sono state usate materie plastiche di scarto o riciclate

Si ricorda che le caratterizzazioni specifiche richieste dalla Farmacopea devono essere effettuate dal trasformatore o dall'utilizzatore finale, in relazione alle condizioni d'uso.

L'utilizzatore deve accertarsi che il manufatto sia idoneo al contatto con i prodotti medico-farmaceutici.

Normative e Certificazioni di Prodotto
Salvatore Minardi

Questa dichiarazione è valida tre anni e sostituisce quelle precedentemente emesse.
REVISIONE 24 Marzo 2011

International Year of CHEMISTRY 2011

polimeri europa spa
Sede Legale: San Donato Milanese (MI) - Piazza Boldrini, 1 - Italia
Capitale sociale interamente versato: Euro 1.553.400.000,00
Codice Fiscale e registro Imprese di Milano 03823300821
Part. IVA IT 01768800748
R.E.A. Milano n. 1351279
Società soggetta all'attività di direzione e coordinamento di Eni S.p.A.
Società con socio unico

POLIMERI EUROPA
DECLARATION OF CONFORMITY TO EUROPEAN PHARMACOPOEIA

RIBLENE F22, F33, F34, FL23, FL30 (produced in Italy), FL 34E, FM 34E, FM53, MP30 (produced in France), MP31, MP31R, FL34D

The products supplied in original container conform for composition to Pharmacopoeia monographs for Polyolefines:

EuPh 3.1.3	Polyolefines (Edition 7th, 2011)
EuPh 3.1.5	Polyethylene with additives for containers for preparations for parenteral use and for ophthalmic preparations (Edition 7th, 2011)
USP 34	Polyethylene containers

No wastes or recycled material is used to produce the mentioned products.

Specific characterization for pharmacopoeias must be performed by the user with respect to conditions of use.

The user must ascertain that the product can be used for contact to pharmaceutical products.

Declaration valid for three years
March 24, 2011

Polyethylene bags

Polymer components: ExxonMobil LD150AC / LD150BW

ExxonMobil Chemical

ExxonMobil LDPE

LD 150 Series

Blown Film Resin

Description

LD 150 series are LDPE grades, offering good blend mechanical properties and stiffness.

Several additive packages are available according to the required surface properties.

Applications

- medium duty shrink film
- shopper bags
- freezer film
- form fill and seal packaging
- general purpose

Additive Package	Antiblock	Slip	Thermal Stabilizer
LD 150BW	No	No	Yes
LD 150AC	450 ppm	500 ppm	Yes

Resin Properties	Test Based On	Typical Value / Unit	
Melt Index	ASTM D 1238	0.75 g/10 min	
Density	ExxonMobil Method	0.923 g/cm^3	
Peak Melting Temperature	ExxonMobil Method	109 °C	228 °F

Film Properties (@ thickness 50 µm (1.97 mil))

Tensile Strength at Break	MD	ASTM D 882	24 MPa	3500 psi
	TD		23 MPa	3350 psi
Elongation at Break	MD	ASTM D 882	370 %	
	TD		570 %	
1% Secant Modulus	MD	ASTM D 882	220 MPa	32000 psi
	TD		260 MPa	37500 psi
Haze		ASTM D 1003	7 %	
Gloss MD, 60°		ASTM D 2457	9 %	
Dart Drop Impact Strength, F50		ASTM D 1709A	175 g	
Elmendorf Tear Strength	MD	ASTM D 1922	200 g	
	TD		200 g	

The film properties have been measured on a 50 µm (1.97 mil) thick film of LD 150BW (Blow-up ratio : 2.5)

LD 150 series can - in principle - be used in food contact applications in various EU Member States and in the USA (FDA). Migration or use limitations may apply. Please contact your ExxonMobil Chemical representative for more detailed information and/or actual compliance certification documents for the specific grade of interest.

Revised August 2006

Antistatic additives

Antistatic additives: Polybatch VLA66 or CESA-Stat 3101

A. Schulman

POLYBATCH® VLA 66

Product Description

POLYBATCH® VLA 66 is an anti-static masterbatch containing a long lasting anti-static agent to eliminate static charges in LDPE, LLDPE and HDPE during processing and end-use applications.

The anti-static agent contained in POLYBATCH® VLA 66 adds little to the slip properties of the base resin; this property is particularly useful for the production of anti-static HEAVY DUTY bags.

POLYBATCH VLA 510 is a modified version of VLA 66 containing an optimized combination of antistatic agent and antiblocking agent. This assures excellent migration of the antistatic agent and a non-sticky surface during longtime storage at temperatures between 20 and 30°C.

General

Material Status	• Commercial: Active		
Availability	• Asia Pacific	• Europe	
Uses	• Masterbatch		
Agency Ratings	• EU 2002/72/EC [1]	• FDA 21 CFR 177.1520	• FDA 21 CFR 177.1520(c) 2.2
Appearance	• Off-White		
Forms	• Pellets		
Processing Method	• Blown Film	• Cast Film	

Physical	Nominal Value (English)	Nominal Value (SI)
Specific Gravity	0.942	0.940 g/cm³
Bulk Density	34.3 lb/ft³	550 kg/m³
Moisture Content	< 1500 ppm	< 1500 ppm

Usage

POLYBATCH® VLA 66 and POLYBATCH® VLA 510 should be added from 1 to 5% depending on the resin type or the thickness of the part.

Film Application	LDPE - LLDPE	2 - 3%
	HDPE	3 - 5%
Moulded Parts	LDPE - LLDPE	2 - 3%
	HDPE	3 - 5%
Bottle Blowing	HDPE	3 - 5%

As all anti-static agents must migrate to the surface to become effective, it may therefore be necessary to modify the printing and/or sealing conditions.

- seal or print preferably in-line with extrusion
- for better printing increase the corona or flame treatment
- slow down sealing speeds
- use polymers with reduced slip content

Page: 1 of 2 Rev. 2010-01-26

POLYBATCH® VLA 66

A. Schulman

Attention

The migration of the antistatic agent may be slowed-down through the use of pigments with high surface area like certain carbon blacks; in the case of high loadings, the antistatic effects may even be inhibited.

Evaluation of the interaction between POLYBATCH® VLA 66 and some Black Polybatches.

Film thickness : 50 µ

Test methods : Surface resistivity according DIN 53482
Charge Decay Time in seconds (Honestmeter)
Determined at 50% RH and 23°C

LDPE (%)	100	100	100	100	100
POLYBATCH ®VLA 66	2	2	2	2	2
POLYBLAK ® BLACK 1850	-	4	6	-	-
POLYBLAK ®BLACK 1423	-	-	-	4	6
Surface Resistance (OHM)					
After production	$3x10^{11}$	$6x10^{14}$	$1x10^{15}$	$1x10^{16}$	$1x10^{16}$
After 1 week	$2x10^{10}$	$4x10^{11}$	$6x10^{12}$	$2x10^{12}$	$1x10^{13}$
After 2 weeks	$1x10^{10}$	$1x10^{11}$	$9x10^{11}$	$4x10^{12}$	$8x10^{12}$
Charge Decay Time (Seconds)					
After production	4	33	60	60	60
After 1 week	0.8	9	21	30	60
After 2 weeks	0.6	2	15	20	28

Particle size:
- Polyblak® 1850 = 60 nanometer
- Polyblak® 1423 = 20 nanometer

Regulatory

BgVV Clearance up to 3% by weight for Non-Fatty foodstuffs.
Detailed information is available upon request.

Packaging & Storage

POLYBATCH® VLA 66 and POLYBATCH® VLA 510 are packed in 25 kg Polyethylene bags on shrink-wrapped pallets. They can be stored up to maximum 6 months at 25°C for optimum performance. Higher temperatures might reduce storage time considerably.

Notes

[1] Commission Directive 2002/72/EC and its successive amendments up to and including 2009/975/EC.

A. Schulman

Food contact declaration

Company	A. Schulman Plastics BVBA Pedro Colomalaan 25 B-2880 Bornem - Belgium T +32-3-890 42 11 ehs@eu.aschulman.com

General info

PRODUCT	**POLYBATCH VLA 66 NATURAL ASBAG 25**
PRODUCT CODE	10720901
VERSION	1.2
ISSUE DATE	26/03/2012
VALID TO	This document is valid until the next relevant legislative,regulatory and /or compositional change.
CONCLUSION EU	The composition complies with the EU legislation when a method has been used to verify that the migration limitation is not exceeded.
CONCLUSION USA	All components comply with FDA, CFR title 21; for the intended use.

European Union

1935/2004/EC	The product is produced in conformity to this frame directive and 10/2011/EC amended up to 1282/2011/EC. . All monomers and additives fulfill the requirements for food contact with following restriction:
Migration Limits	FCM No 433 - Ref No 68320 - ANTI-OXYDANT - 6 mg/kg SML FCM No 19 - Ref No 39090 - ANTI-STATIC - 1,2 mg/kg SML (T), expressed as tertiary amine
Dual use additives	FCM No 139 - Ref No 14680 & 44160 FCM No 504 - Ref No 86240 - ANTI-BLOCKING FCM No 638 - Ref No 23590 & 76960 - LUBRICANT

USA

Polymers and additives	meet FDA 21 CFR §177.1520(c)3.1a, FDA 21 CFR §177.1520, FDA 21 CFR §177.1520(c)3.2a, FDA 21 CFR §177.1520(c)2.2, FDA 21 CFR §177.1520(c)2.1, FDA 21 CFR §178.2010, FDA 21 CFR §178.3297, FDA 21 CFR §178.3130 At maximum addition of 2,1%

Responsibility	Appropriate overall and specific migration tests on the final material or article will determine the regulatory suitability for contact with different food types and various end-use conditions.However these are beyond the control of A. SCHULMAN and are a part of the

Masterbatches

Technical Product Information

Clariant

Exactly your chemistry.

CESA®-stat 3101

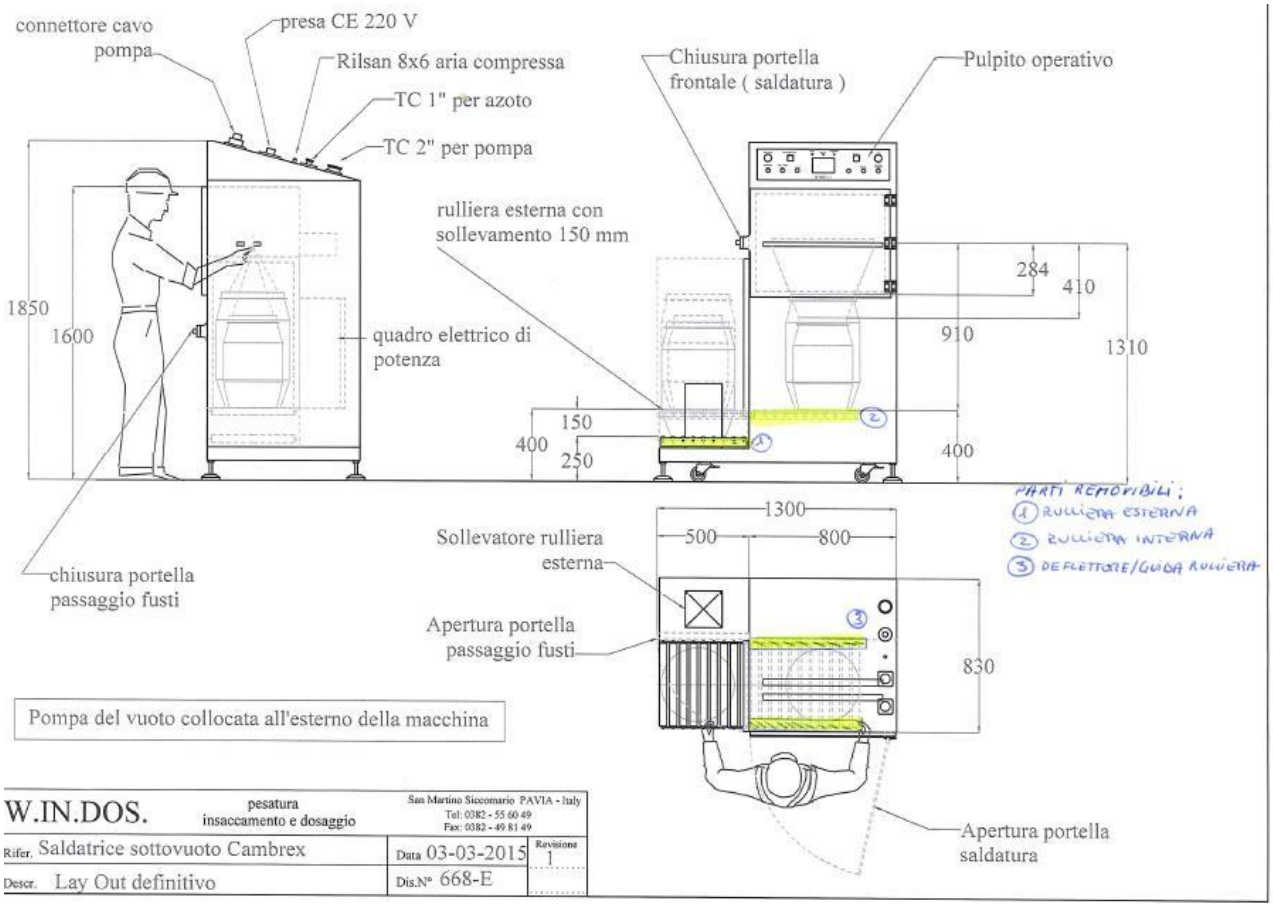
General	Most thermoplastic polymers are electrically non-conductive and have a strong tendency to accumulate surface electrostatic charges. Undesired or dangerous effects are dust attraction, difficult opening of bags, and static discharge. The addition of CESA®-stat masterbatches reduces the surface resistance of thermoplastic polymers and avoids the accumulation of static charges.
Description	CESA®-stat 3101 is a concentrate of antistatic agents in pellet form. It contains amine-based antistatic agents in a PE carrier.
Phisycal Form	Pellets
Bulk Density	0,52 Kg/dm^3
Volatiles	< 0,3 %
Applications	Film extrusion, blow moulding, injection moulding of LDPE, LLDPE, EVA, HDPE. CESA-stat 3101 can also be used in PP extrusion and injection moulding applications.
Benefits	None or very low influence on heat sealing and printing operations. Long-term antistatic effect.
Dosage	0,5 % - 1,5 % in LDPE, LLDPE and EVA applications. 1 % - 2 % in HDPE applications. 2,5 % - 3,5 % in PP applications.
Packaging	20 kg valve type PE bags
Remarks	The antistatic effect reaches its optimum level after a period of time (2 – 7 days , depending on the polymer in use, article thickness, dosing ratio) Excessive addition of antistatic agents may cause problems of heat sealing and printing. These operations should be carried out soon after the production of the end article. The product should be stored in a cool and dry place, away from direct sunlight.

Created: 11 July 2006
Changed: Jul-06
Page 1 / 1

Clariant Masterbatches (Italia) S.p.A.
Via Lainate, 26
I – 20010 Pogliano Milanese (MI)
T: +39 02 9918 7558
F: +39 02 9918 7552
http://www.clariant.masterbatches.com
italy.mb.marketing@clariant.com

Via Piave, 12
I – 23871 Lomagna (LC)
T: +39 02 9918 4699
F: +39 039 53 00 295

Pulse welder



- The welder external vertical structure is composed of stainless steel AISI 304 with the ground support area of 750x800 mm and the height of 1850 mm, with support adjustable feet.
- The welder is equipped with two operating accesses: a lateral access 950x530 mm equipped with an external roller track with lifter, in order to facilitate the inclusion of various size drums, a front door 600x800 mm provided with glass of 100x200mm.
- The fixed roller and sealing bars are located within the welding's room.
- The command and the operator panel for the control of the welding operations are located in the high part head on.
- The electric circuits and system control are located in the electric panel in the rear of the cab.
- The sealing bars with related support will be constructed in order to facilitate a quick disassembly for cleaning operations.
- The internal structure of the cab has satin surface and it is realized in order to facilitate the cleaning operations.

Plastic drums (HDPE)

6 LITRE WIDE NECK DRUM

CurTec

Plastic drum with screw lid closure
for pharmaceuticals, specialty chemicals and food ingredients

Protect your valuable products against moisture, tampering and contamination
Make sure your hazardous solids arrive safely at their destination
Comply with food safety legislation

Product code	7006
Capacity	6 litres / 1.6 US gallons
Diametre opening	136 mm
Diametre drum	198 mm
Total height	263 mm
Material	HDPE
Lid color	■
Drum colour	
Tamper evident feature	✔
UN marking	1H2/X20/S/--/NL/CURTEC 1352
Handgrips	–
Food grade	✔
Screw lid	✔
Water tight	✔
Pallet quantity	240 pcs
Stock item	✔

17 LITRE TOTAL OPENING DRUM

CurTec

Plastic drum with screw lid closure
for pharmaceuticals, specialty chemicals and food ingredients

Protect your valuable products against moisture, tampering and contamination
Make sure your hazardous solids arrive safely at their destination
Comply with food safety legislation

Product code	6945
Capacity	17 litres / 4.5 US gallons
Diametre opening	295 mm
Diametre drum	338 mm
Total height	252 mm
Material	HDPE
Lid color	■
Drum colour	
Tamper evident feature	✔
UN marking	1H2/X25/S/--/NL/CURTEC 360
Handgrips	–
Food grade	✔
Screw lid	✔
Water tight	✔
Pallet quantity	81 pcs
Stock item	✔

QUALITY ASSURANCE

Regulatory Affairs Data Sheet

Manufacture

All our products are of Dutch origin and manufactured in our plant in Rijen (The Netherlands). Our management system includes:

- NEN-EN-ISO 9001: 2015
- NEN-EN-ISO 14001: 2015
- FSSC 22000: version 3, 2013
- NEN-EN-ISO 15378:2015

Our management system is annually audited by Lloyd's Register Quality Assurance.

Food contact

All our drums, Click Packs and Packos with a food safe logo comply with the following regulation:

- EC regulation 1935/2004 (Materials and articles intended to come into contact with food)
- EC regulation 10/2011 (on plastic materials and articles intended to come into contact with food including amendment EC 2015/174)
- EC regulation 2023/2006 (Good Manufacturing Practice applicable to all food contact materials)
- EC directive 94/62
- FDA regulation CFR 21 177.1520 (Olefin polymers)

Toxins

Heavy metals
All our drums, Click Packs and Packos comply with EC regulation 94/62. In addition, our products have the potential to be recycled according to these requirements.

Phthalates
All our drums, Click Packs and Packos meet the requirements for phthalates. To the best of our knowledge (based on the available documentation from raw materials suppliers), phthalates are not intentionally used, or added, in the manufacture of our PE products. Thermoplastic elastomer sealing gaskets may contain traces of phthalates but fully comply with EU Regulation 10/2011 and EC Regulation 1907/2006 concerning REACH.

Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE)
All our drums, Click Packs and Packos are to be considered safe with respect to BSE and TSE.

Genetic Modified Organism (GMO)
All our drums, Click Packs and Packos are to be considered safe with respect to GMO.

CurTec
HIGH PERFORMANCE PACKAGING

Bisphenol
All our drums, Click Packs and Packos comply with EC regulation 10/201.
To the best of our knowledge, based on the declarations from our suppliers, Bisphenol is not intentionally added.
Based on this information our Drums, Click Packs and Packos are considered to be in compliance with the French law No 2012-1442.

BADGE, NODGE and BFDGE
Epoxy derivates (BADGE, NODGE and BFDGE) are not intentionally added to the raw materials used for the production of our drums, Click Packs and Packos.

Dimethylfumarate (DMF)
Dimethylfumarate is not intentionally added to the raw materials used for the production of our drums, Click Packs and Packos.

Ozone depleting chemicals (ODCs)
Ozone depleting chemicals are not intentionally added to the raw materials used for the production of our drums, Click Packs and Packos.

Melamine
Melamine is not intentionally added to the raw materials used for the production of our drums, Click Packs and Packos.

Dioxins/ Furans/ PCBs
Dioxins/ Furans/ PCBs are not intentionally added to the raw materials used for the production of our drums, Click Packs and Packos.

Pharma

US Food and Drug Administration (FDA)
All our drums, Click Packs and Packos with a food safe symbol comply with FDA Type III CFR 21regulations and are included in the Drug Master File #16388.

REACH

Our products do not contain items which fit the description of Substances of Very High Concern (SVHC) with more than 0.1 mass percentage which are listed in the present (candidate) list which is published by the ECHA.

CurTec
HIGH PERFORMANCE PACKAGING

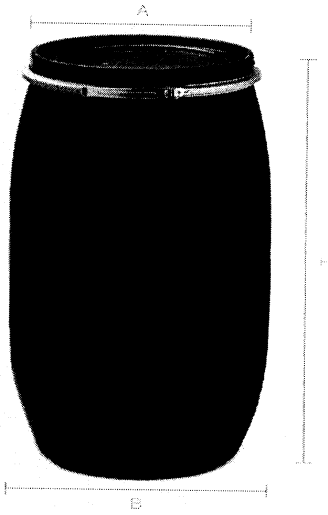
FUSTIPLAST GREIF

www.fustiplast.com

TECHNICAL DATA SHEET
OH IT 110 UN FOOD

4,7

BODY		
Material	Hight density high molecular weight Polyethylene	
Manufacturing process	Extrusion blow-moulding	
Weight	3,3 kg	
Total Capacity TC	113,5 l.	
Brimful capacity BC	119 lt	
Standard colours	Blue	
Handling	----	
Stacking height up to 25°C * with density	1 + 2 1,4 Kg/l	1 + 1 1,8 Kg/l



LID	
Manufacturing process	Injection Molding
Weight	0,87 kg
Colour	Black
Gasket	TPE for food
Notes	

CLOSURE	
Type	Ring
Material	Galvanized steel
Weight	0,48 Kg.
Seal	Available

UN HOMOLOGATIONS
1H2/X 150/S

OTHER INFORMATION	
Food suitability	Verify suitability
Minimum lot	1500
Amount per pallet	18
Venting devices	On request

DIMENSIONS		mm.
Drum Diameter	B	480
Height	H	754
Opening Diameter	A	395

* These figures only apply when drums are filled to 98% of their capacity and stacked on reversible flat pallets. The bottom surface must cover at least 80% of the top area.

- Measurements made in accordance with standards EN 12714 and ISO 20848
- Please read our instruction manual published on our web site www.fustiplast.com
- Food contact: verify suitability to your needs, more details in document "STATEMENTS AND METHODS FOR USE WITH FOOD". It may be necessary to use the drum as a secondary package.

REVISION C.3 02/06/2015 | Issued and approved by Sales Manager | TOLERANCES DIN 16901

FUSTIPLAST GREIF	STATEMENTS AND METHODS FOR USE WITH FOOD	Rel. 11 dated 10 march 2015	Written and approved by QA

Messrs. CAMBREX PROFARMACO MILANO SRL

Issued by: **Greif Plastics Italy Srl Viale Industria, 29 Bottanuco 24040 (BG) ITALY**

Subject: "Tight Head" drums supplied to your firm, identified by the item code

TH120TS1A0011 - TH220TS2A0067 -TH060TS1A0108

Raw material (HDPE) complies with:

to the following European comunity laws:	Regulation 1935/2004/EC Regulation 1895/2005/EC REGULATION (EU) No 10/2011 aand following modifications and updates
	Directive 2002/72/EC and following updates
and to the following italian laws:	DPR 777/82 and following modifications and updates DM 21/03/1973 and following modifications and updates
FDA	21 CFR 177.1520(a)(2)(i) and (c)2.2

Raw material (HDPE) contains following substances subject to SML:
- PM Ref : 18820 - CAS RN : 00592-41-6 SML= 3 ppm
- PM Ref : 68320 - CAS RN : 2082-79-3 SML= 6 ppm

Product is eligible for transportation of substances at room temperature under conditions similar to migration testing carried out at 40 degrees for 10 days (OM2). The user must verify that the container is not used improperly (eg heating products, exposure to high temperatures, etc.).

The overall migration limits, together with specific restrictions about monomers and / or additives present in the material, are respected for all foods, in the conditions of use mentioned above. The claim is supported by the statements of suppliers of raw materials (HDPE), from analytical tests carried out in accordance with the directives 82/711/EEC and 85/572/EEC and DM 21/03/1973 and / or under to calculations made taking into consideration the content of substances subject to limits migration. The calculations were made assuming that 1 kg of food is in contact with 6 dm2 of packaging material

Our production process is conform to COMMISSION REGULATION (EC) No 2023/2006 of 22 December 2006 on good manufacturing practice for materials and articles intended to come into contact with food.

The raw material (HDPE) may contain substances regulated by regulations (EC) 1333/2008 and (EC) 1334/2008 (additives and flavouring for food). According to experimental data and / or theoretical calculations such substances comply with the provisions of art. 9 paragraph 3 of regulation (EU) 10/2011.
The user of the material intended for contact with food has a responsibility to inform the company writing any restrictions because of the compositional (presence of additives and flavorings) of food to pack.

The raw materials used are in conformity with the Directive 94/62/EC of the European Parliament and Council, dtd December 20th 1994 and following updates, regarding packaging and packaging wastes, as declared in our suppliers' certificates; during the manufacturing process, there is no addition of heavy metals such as lead, cadmium, mercury and chromium.

Recycled raw materials: in the production of food containers are not used recycled materials.

The suitability of packaging for food applications does not guarantee any organoleptic compatibility with therein filled product; such compatibility must hence be verified individually under container user responsability.

The requirement of suitability of container for the transport of food substances or substances intended to come into contact with substances for personal use, must be formally specified on each purchase order.

The absence of contamination by pathogens can be obtained only for targeted productions, produced on specific customer request, controlled from production to delivery to the customer, but in any case, who fills contenitors must verify that hygienic conditions of the containers are appropriate and/or provide for any necesary action of cleaning / sanitizing.

page 1 of 2

FUSTIPLAST GREIF	STATEMENTS AND METHODS FOR USE WITH FOOD	Rel. 11 dated 10 march 2015	Written and approved by QA

Messrs. CAMBREX PROFARMACO MILANO SRL

Issued by: **Greif Plastics Italy Srl Viale Industria, 29 Bottanuco 24040 (BG) ITALY**

Subject: "Tight Head" drums supplied to your firm, identified by the item code

TH120TS1A0011 - TH220TS2A0067 -TH060TS1A0108

The user must verify that the container is not used improperly (eg heating products, exposure to high temperatures, etc.).

Do not expose containers to sun

Further informations

BSE-TSE: Components derived from animal sources are not used in the manufacture or formulation of raw materials.

Halal/Kosher: Components derived from animal sources are not used in the manufacture or formulation of raw materials.

Allergen: are not intentionally used in the manufacture of or formulation of raw material

Phtalate: are not intentionally used in the manufacture of or formulation of raw material

Nanomaterials: are not intentionally used in the manufacture of or formulation of raw material

Epoxy derivatives: The materials BADGE, BFDGE or NOGE are not intentionally used in the manufacture or formulation of raw materials as referenced in Commission Regulation 1895/2005/EC

Bisphenol A: Bisphenol A is not intentionally used in the manufacture or formulation of raw materials.

This CONFORMITY DECLARATION is valid for the period of one year from the date of emission and will be updated if important changes in container manufacturing able to change conformity requests will arise, or when law references specified in point 1 will be modified and updated

Date 30/09/2015

Sergio Pariscenti

page 2 of 2

BAM
Bundesanstalt für Materialforschung und -prüfung

ZULASSUNGSSCHEIN

CERTIFICATE OF APPROVAL

1. Neufassung / *Revised version no. 1*

Nr. D/BAM 11648/1H2

für die Bauart einer Verpackung zur Beförderung gefährlicher Güter
for the design type of a packaging for the transport of dangerous goods

Aktenzeichen / *Reference no.* III.12/202245

Vom Bundesministerium für Verkehr, Bau und Stadtentwicklung nach § 6 Abs. 5 der Gefahrgutverordnung See in Verbindung mit Kapitel 7.9 des IMDG-Codes bestimmte zuständige Behörde Deutschlands

Competent German authority, authorised by the Federal Ministry of Transport, Building and Urban Affairs in acc. with § 6 para. 5 of the Regulation on the Transport of Dangerous Goods by Sea in conjunction with chapter 7.9 of the IMDG-Code

1. Rechtsgrundlagen / *Legal bases*

1.1 Gefahrgutverordnung Straße, Eisenbahn und Binnenschifffahrt – GGVSEB in der Fassung der Bekanntmachung vom 17. Juni 2009 (BGBl. I S. 1389)
(German regulation concerning the transport of dangerous goods by road, rail and inland waterways)

1.2 Gefahrgutverordnung See – GGVSee in der Fassung der Bekanntmachung vom 3. Dezember 2007 (BGBl. I, S. 2815), zuletzt geändert durch die Zweite Verordnung zur Änderung der Gefahrgutverordnung See vom 22. Dezember 2009 (BGBl. I, S. 3967), insbesondere der International Maritime Dangerous Goods Code (IMDG Code), geändert durch die Entschließung MSC.262(84), in der amtlichen deutschen Übersetzung bekannt gegeben am 28. Februar 2009 (VkBl. 2009 S. 102)
(German regulation concerning the transport of dangerous goods by sea)

1.3 Luftverkehrs-Zulassungs-Ordnung (LuftVZO) in der Neufassung vom 10. Juli 2008 (BGBl. I S. 1229), zuletzt geändert durch die Verordnung vom 2. Oktober 2009 (BGBl. I, S. 3535)
(German regulation concerning the transport of dangerous goods by air)

2. Zulassungsinhaber / *Approval holder*

FUSTIPLAST IMBALLAGGI SOFFIATI IN PLASTICA
V.le Industria 33
I - 24040 Bottanuco (BG)

3. Hersteller / *Manufacturer(s)*

	Kurzzeichen/*Identification*
FUSTIPLAST Germany GmbH, In der Lach,D - 66271 Kleinblittersdorf	**FPLD**
FUSTIPLAST IMBALLAGGI SOFFIATI IN PLASTICA, V.le Industria 33, I - 24040 Bottanuco (BG)	**FPL**
Plastinova Italiana S.p.A., Via Patrioti, I - 25014 Castenedolo (Brescia) Italia	**PI**

4. Beschreibung der Bauart / *Specification of the design type*

Fass aus Kunststoff mit abnehmbarem Deckel / *Plastics drums removable head*

Hersteller-Typenbezeichnung / *Type designation of the manufacturer:* -

Abmessungen / *Dimensions:*

Außendurchmesser über Rumpf / *Diameter, body*	[mm]	498
Höhe (gesamt) / *Height, total*	[mm]	974
Behältermasse / *Tare mass*	[kg]	5,1
Fassungsraum / *Capacity*	[l]	161

Spezifikation / *Specification*:

Die Bauart wird durch die Beschreibungen, technischen Zeichnungen, Werkstoffspezifikationen und Bescheinigungen gemäß der/des unter Ziffer 5 genannten Prüfnachweise(s) festgelegt.
The design type is specified by the descriptions, technical drawings, material specifications and certificates as given in the test report(s), referred to under no. 5.

Seite 2 zum Zulassungsschein Nr. D/BAM 11648/1H2 - 1. Neufassung vom 19. Juli 2010

Page 2 of the Certificate of Approval no. D/BAM 11648/1H2 - Revision no. 1

5. Prüfnachweise / *Performance Proofs*

Prüfbericht Nr. *Test report no.*	Nachtrag Nr. *Amendment no.*	Datum *Date*	Prüfstelle *Testing institute*
070021/3	0	08.01.2007	TÜV Rheinland Industrie Service GmbH, Regionalbereich Berlin/ Brandenburg/ Mitte, Abteilung Verpackung und Gefahrgut, Köthener Straße 33, D - 06118 Halle/S
070021/3	1	15.06.2010	

6. Bauartzulassung / *Design Type Approval*

Die unter Ziffer 4 und 5 beschriebene Bauart erfüllt die Vorschriften nach Ziffer 1. Die Bauart wird mit den in Ziffer 9 genannten Nebenbestimmungen für die Beförderung gefährlicher Güter zugelassen.
The design type as specified under no. 4 and 5 complies with the regulations under no. 1. Herewith, the design type is declared as approved with the subsidiary regulations as given under no. 9 for the transport of dangerous goods.

Diese 1. Neufassung ersetzt den Zulassungsschein Nr. D/BAM 11648/1H2 vom 13. Februar 2007.
This revision no. 1 replaces the Certificate of Approval no. D/BAM 11648/1H2 dated 13. February 2007.

Die Eignung der Bauart für die Beförderung gefährlicher Güter gilt bei Einhaltung der folgenden Grenzwerte bzw. Einschränkungen als erbracht:
The suitability of this design type for the transport of dangerous substances is only valid under the following limiting conditions:

- Verwendung für gefährliche feste Güter der Verpackungsgruppen I, II oder III
  Use for solid dangerous substances of Packaging Groups I, II or III

max. Bruttomasse / *Maximum gross mass*	[kg]	240
max. Schüttdichte / *Maximum bulk density*	[kg/l]	1,53
min. Schüttwinkel / *Minimum angle of repose*	[°]	38

- vergleichbare oder günstigere Eigenschaften der Füllgüter in Bezug auf ihre Schädigungswirkung bei der Fallprüfung entsprechend dem(n) verwendeten Prüffüllgut (-gütern)
  Equivalent or better Properties of the filling substances with regard to the effect of damage of the package performing the drop test in comparison with the used substance(s) during the performed design type tests

7. Fertigung von Verpackungen / *Manufacturing of packagings*

Nach der zugelassenen Bauart dürfen Verpackungen serienmäßig gefertigt werden. Der Hersteller muss gewährleisten, dass die serienmäßig gefertigten Verpackungen die festgelegte Spezifikation der Bauart erfüllen.
The packagings may be manufactured in series according the approved design type. The manufacturer has to guarantee that packagings manufactured in series comply with the approved design type.

8. Kennzeichnung / *Marking*

Die nach der zugelassenen Bauart serienmäßig gefertigten Verpackungen sind wie folgt zu kennzeichnen:
Packagings manufactured in series to the approved design type shall be marked as follows:

u
n

1H2/X240/S/../D/BAM 11648-**

In den Freiraum sind Monat und Jahr (jeweils die letzten zwei Stellen) der Herstellung einzutragen.
The space shall be used to insert the month and the year (last two digits) of manufacture.

**) Angabe des festgelegten Kurzzeichen des jeweiligen Herstellers gemäß Ziffer 3
Insertion of the specified identification of the respective manufacturer according to no. 3

Seite 3 zum Zulassungsschein Nr. D/BAM 11648/1H2 - 1. Neufassung vom 19. Juli 2010

Page 3 of the Certificate of Approval no. D/BAM 11648/1H2 - Revision no. 1

9. Nebenbestimmungen / *Subsidiary Regulations*

9.1 Befristungen / *Limitations*

entfällt / *not to apply*

9.2 Bedingungen / *Conditions*

entfällt / *not to apply*

9.3 Widerruf / *Withdrawal*

Diese Zulassung wird unter dem Vorbehalt des jederzeitigen Widerrufs erteilt. Ein hinreichender Grund für den Widerruf ist z.B. ein Verstoß gegen die Auflage gem. Ziffer 9.4.1.
This approval is liable to withdrawal at any time. For instance, violation of the obligation no 9.4.1 is a sufficient reason for the withdrawal.

9.4 Auflagen / *Obligations*

9.4.1 Der Hersteller darf die Kennzeichnung nach Ziffer 8 dieser Zulassung an Verpackungen nur dann anbringen, wenn diese der zugelassenen Bauart entsprechen und nach einem von der BAM anerkannten und überwachten Qualitätssicherungsprogramm hergestellt und geprüft werden.
The manufacturer is allowed to apply the marking as specified in no. 8 to packagings only if they comply with the approved design type and are manufactured and tested under a quality assurance programme as recognised and controlled by BAM.

9.4.2 Der in Ziffer 2. genannte Zulassungsinhaber muss nachweisbar sicherstellen, dass alle Bestimmungen und Hinweise dieses Zulassungsscheins über eine ordnungsgemäße Verwendung der Verpackungen demjenigen, der diese Verpackungen für gefährliche Güter verwendet bzw. mit gefährlichen Gütern befüllt, zur Kenntnis gebracht werden.
The approval holder in no. 2 must make proof that all regulations and notices of this approval governing the use of packagings for the transport of dangerous goods have to be made known to every user.

10. Hinweise / *Notices*

10.1 Die Zulässigkeit der Verwendung von Verpackungen der zugelassenen Bauart bezüglich der Verpackungsart, der Innenverpackungen, des Fassungsraums bzw. der Masse richtet sich nach den Bestimmungen der jeweils zutreffenden Rechtsvorschriften für die einzelnen Verkehrsträger. Alle sonstigen Vorschriften (z. B. Füllgrad, Verträglichkeit mit den Verpackungswerkstoffen) für die Beförderung gefährlicher Güter in der zugelassenen Verpackungsbauart bleiben unberührt.
The use of packagings of the approved design type with respect to packaging type, inner packaging(s), capacity or mass is regulated by the respective modal regulations. Any other requirements (e.g. filling degree, compatibility with packaging materials) for the transport of dangerous goods by the approved packaging design type are to be taken in account.

10.2 Die Bauart erfüllt die Prüfanforderungen für Verpackungen zur Beförderung gefährlicher Güter der folgenden internationalen Bestimmungen in den zum Zeitpunkt der Ausstellung des Zulassungsscheins jeweils gültigen Ausgaben:
The design type complies with the test provisions of the following international regulations for packagings for the transport of dangerous goods which in every case are valid at the date of issue of this certificate of approval:

- Europäisches Übereinkommen über die internationale Beförderung gefährlicher Güter auf der Straße **(ADR)**
  *The European Agreement Concerning the International Carriage of Dangerous Goods by Road **(ADR)***
- Ordnung für die internationale Eisenbahnbeförderung gefährlicher Güter **(RID)**
  *The Regulations on the International Transport of Dangerous Goods by Rail **(RID)***
- International Maritime Dangerous Goods Code (IMDG Code)
  The International Maritime Dangerous Goods Code (IMDG Code)
- RECOMMENDATIONS ON THE TRANSPORT OF DANGEROUS GOODS der UNITED NATIONS
  The RECOMMENDATIONS ON THE TRANSPORT OF DANGEROUS GOODS of the UNITED NATIONS
- ICAO Technical Instructions, ebenfalls niedergelegt in den IATA-Dangerous Goods Regulations
  The TECHNICAL INSTRUCTIONS FOR THE SAFE TRANSPORT OF DANGEROUS GOODS BY AIR (ICAO-TI) similarly written down in the IATA-Dangerous Goods Regulations (IATA-DGR)

Seite 4 zum Zulassungsschein Nr. D/BAM 11648/1H2 - 1. Neufassung vom 19. Juli 2010

Page 4 of the Certificate of Approval no. D/BAM 11648/1H2 - Revision no. 1

10.3 Diese Zulassung wird auf der Internetseite der Bundesanstalt für Materialforschung und -prüfung, Berlin (www.bam.de oder www.tes.bam.de) veröffentlicht.
This approval will be published in due time on the Internet (www.bam.de or www.tes.bam.de) by the Federal Institute for Materials Research and Testing, Berlin.

11. Rechtsbehelfsbelehrung / *Rights of legal appeal*

Gegen diesen Bescheid kann innerhalb einer Frist von einem Monat nach Zustellung schriftlich oder zur Niederschrift bei der BAM Bundesanstalt für Materialforschung und -prüfung, Unter den Eichen 87, 12205 Berlin Widerspruch eingelegt werden. Die Frist ist nur dann gewahrt, wenn der Widerspruch vor Fristablauf bei der BAM eingeht.
Legal appeal may be raised against this notification within a respite of one month after delivery date. The appeal has to be submitted to the BAM Federal Institute for Materials Research and Testing, Unter den Eichen 87, 12205 Berlin, in writing or for record. To keep the term, the appeal has to arrive at the BAM before the respite ends.

12200 Berlin, 19. Juli 2010

Fachgruppe III.1
Gefahrgutverpackungen
Im Auftrag / *For*

Dipl.- Ing. B.-U. Wienecke

BUNDESANSTALT FÜR MATERIALFORSCHUNG UND -PRÜFUNG (BAM) 39

Arbeitsgruppe
Zulassung und Verwendung
Im Auftrag / *For*

Dipl. - Ing. (FH) D. Teutschbein

(Dieser Zulassungsschein besteht aus 4 Seiten.)
(This approval covers 4 pages.)

Certificate

Standard **ISO 9001:2008**

Certificate Registr. No. 01 100 087744

Certificate Holder:

Greif Plastics Italy S.r.l.
Viale Industria, 29
I - 24040 Bottanuco (BG)

including the locations according to annex

Scope: Design and Production of blow-moulded jerricans, drums, IBCs and packages made from plastic

Proof has been furnished by means of an audit that the requirements of ISO 9001:2008 are met.

The due date for all future audits is 28-07 (dd.mm).

Validity: The certificate is valid from 2014-08-26 until 2017-07-30.
First certification 1999

2014-08-27

TÜV Rheinland Cert GmbH
Am Grauen Stein · 51105 Köln

DAkkS
Deutsche Akkreditierungsstelle
D-ZM-16031-04-00

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Annex to certificate

Standard **ISO 9001:2008**

Certificate Registr. No. 01 100 087744

No.	Location
/02	**Greif Plastics Italy S.r.l.** **Werk Bottanuco** Viale Industria 29 I - 24040 Bottanuco (BG)
/03	**Greif Plastics Italy S.r.l.** **Werk Castenedolo** Via Patrioti 94/96 I - 25014 Castenedolo (BS)
/04	**Greif Plastics Germany GmbH** **Werk Kleinblittersdorf** In der Lach D - 66271 Kleinblittersdorf
/05	**Greif Plastics Germany GmbH** **Werk Hückelhoven** Benzstrasse 2 D - 41836 Hückelhoven

2014-08-27

TÜV Rheinland Cert GmbH
Am Grauen Stein · 51105 Köln

DAkkS Deutsche Akkreditierungsstelle D-ZM-16031-04-00

Page 1 of 1

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CSI
CERTIFICAZIONE E TESTING

DIVISIONE: *DIVISION:* **FOOD PACKAGING MATERIALS** LABORATORIO: *LABORATORY:* **FOOD CONTACTS**

RAPPORTO DI PROVA
(Test Report)

Pag. 1 di/*of* pag. 8

N° 0164\FPM\FDC\13

Data: *Date:* 28/02/2013

IDENTIFICAZIONE E DESCRIZIONE DEL CAMPIONE:
SPECIMEN DESCRIPTION:

CONTAINER BLUE HDPE 56020S

DATI IDENTIFICATIVI DEL CLIENTE:
CLIENT:

FUSTIPLAST srl
VIALE INDUSTRIA, 29
24040 BOTTANUCO (BG)

NORMA DI RIFERIMENTO:
REFERENCE STANDARD:
D.P.R. 777 dated 23/08/1982, D.L. 108 dated 25/01/1992, D.M.34 dated 21/3/73
European Directives: 82/711/EEC GUCEE L 297 dated 23/10/82, 85/572/EEC GUCEE L 372 dated 31/12/1985, 93/8/EEC GU L90 dated 14/04/1993, 97/48/EC GUCE L 222 dated 12/8/97. Regulations 1935/2004/EC GUCE L 338 dated 13/11/04 and 1895/2005/EC GUCE L 302 dated 19/11/2005. Regulations 10/2011/EU, 321/2011/EU and 1282/2011/EU.
UNI EN 1186 1÷15:2003.

DISTRIBUZIONE ESTERNA: *OUTSIDE DISTRIBUTION:*	DISTRIBUZIONE INTERNA: *INSIDE DISTRIBUTION:*
FUSTIPLAST srl	Copy to Division Head

ENTE DI ACCREDITAMENTO:
ACCREDITATION BODY:

Mod.37 - Rev. 0 - Società a Socio Unico soggetto ad attività di direzione e coordinamento di IMQ spa

CSI CERTIFICAZIONE E TESTING	RAPPORTO DI PROVA *(Test Report)*	Pag. di/*of* pag.	2 / 8
	N° 0164\FPM\FDC\13	Data: *Date:*	28/02/2013

GENERALITIES

- Sample receiving date: 18/10/2012
- Analysis start date: 22/10/2012
- Analysis end date: 09/11/2012
- Deviation from test methods: NO

SAMPLE DESCRIPTION

CONTAINER BLUE HDPE 56020S

SAMPLING

The initial sampling has been done by the customer.
The sampling for the test has been done drawing casually part of the sample in our possession.

DECLARATION

The test results of the present report are related exclusively to the tested sample.
The present test report cannot be partially reproduced without the authorization of CSI managing Director.
The uncertainties are estimated as extended uncertainty obtained multiplying the standard uncertainty by the coverage factor k corresponding to a confidence level of about 95%. Normally, this factor = 2.
This report is the English translation of the test report 1144\FPM\FDC\12_1 dated 20/11/2012.

PERFORMED DETERMINATIONS

1) DETERMINATION OF THE OVERALL MIGRATION

Verification of the suitability of articles and materials to be employed in contact with foodstuffs, according to D.P.R. 777 dated 23/08/1982, D.L. 108 dated 25/01/1992, D.M.34 dated 21/3/73 European Directives: 82/711/EEC GUCEE L 297 dated 23/10/82, 85/572/EEC GUCEE L 372 dated 31/12/1985, 93/8/EEC GU L90 dated 14/04/1993, 97/48/EC GUCE L 222 dated 12/8/97. Regulations 1935/2004/EC GUCE L 338 dated 13/11/04 and 1895/2005/EC GUCE L 302 dated 19/11/2005. Regulations 10/2011/EU, 321/2011/EU and 1282/2011/EU.
UNI EN 1186 1÷15:2003.

Food simulant	Contact condition
Acetic acid in aqueous solution 3% w/v	10 days at 60°C
Ethylic alcohol 95% V/V in aqueous solution	10 days at 60°C
Rectified olive oil	10 days at 60°C

Mod. 38 - Rev. 6

GRUPPO IMQ

	RAPPORTO DI PROVA *(Test Report)*	Pag. di/*of* pag.	3 8
CSI CERTIFICAZIONE E TESTING	N° 0164\FPM\FDC\13	Data: *Date:*	28/02/2013

Migration test was carried out by **Total immersion**.
LOD (limit of detection): 1 mg/dm^2.

2) QUANTITATIVE DETERMINATION OF PRIMARY AROMATIC AMINES: METHOD L.00.00-6 (LMBG § 35)

The procedure used to quantify the primary aromatic amines was a spectrophotometer method, based on the colour complex formed by a diazotization and a coupletization reaction. The solution was further concentred and eluted on a solid phase column. The final solution was photometrically detected at 550 nm (Method BGVV § 64 LFGB, L.00.00-6 dated 1995, updated 2002)
An external calibration curve detected at 550 nm was used to quantify the primary aromatic amines. An aniline standard solution 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 g in acetic acid 3% was detected.
LOD: 0.2 µg /100 ml or LOD: 0.002 mg/kg or LOD: 0.0003 mg/dm2 (the limit is originally expressed in mg/kg; it is possible to convert the measure unit by dividing for the factor 6 to express them in mg/dm2.)

3) SPECIFIC MIGRATION OF BA, CO, MN, ZN, CU, FE, LI

Determination of the specific migration of Ba, Co, Mn, Zn, Cu, Fe, Li according to Reg. EU 10/2011 from the tested material into the simulants by ICP (Inductively Coupled Plasma) technique. The quantitative evaluation was carried out by external calibration of the elements in the same liquid simulants.
Ba - SML: 1 mg/kg; LOD: 0.02 mg/kg
Co - SML: 0.05 mg/kg; LOD: 0.02 mg/kg
Mn - SML: 0.6 mg/kg; LOD: 0.02 mg/kg
Li - SML: 0.6 mg/kg; LOD: 0.02 mg/kg
Zn - SML: 25 mg/kg; LOD: 1 mg/kg
Cu - SML: 5 mg/kg; LOD: 1 mg/kg
Fe - SML: 48 mg/kg; LOD: 1 mg/kg

4) SPECIFIC MIGRATION OF 1-HEXENE

Determination of the specific migration of 1- HEXENE (CAS Nr. 000592-41-6 - Rif. Nr. 18820) from the tested material into the simulant by Head Space/Gas Chromatography/Mass Spectrometer analysis. The quantitative evaluation is carried out by external calibration of 1-HEXENE in the same liquid simulant.
SML: 3 mg/kg.
LOD: 1 mg/kg.

Mod. 38 - Rev. 6

GRUPPO IMQ

CSI CERTIFICAZIONE E TESTING

RAPPORTO DI PROVA *(Test Report)* | Pag. 4 di/*of* pag. 8

N° 0164\FPM\FDC\13 | Data: *Date:* 28/02/2013

5) DETERMINATION OF THE SPECIFIC MIGRATION OF OCTADECYL 3-(3,5-DI-TERT-BUTYL-4-HYDROXYPHENYL)PROPIONATE (CAS 2082-79-3)

Determination of the specific migration of OCTADECYL 3-(3,5-DI-TERT-BUTYL 4-HYDROXYPHENYL)PROPIONATE into the concentrated simulant by GC-MS analysis.
The quantitive evaluation was carried out by an external calibration of 3-(3,5-di-tert-butyl-1-4-hydroxyphenyl)propionate in the same liquid simulant.
SML: 6 mg/kg
LOD: 1 mg/kg

RESULTS

1) DETERMINATION OF THE OVERALL MIGRATION

CONTAINER BLUE HDPE 56020S			
Food simulant: **Acetic acid in aqueous solution 3% w/v**			
Contact condition: **10 days at 60°C**			
Measured unit: **mg/dm²**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Regulation 10/2011/EC)
< 1	<1	--	10 (+ 2)
< 1			
< 1			

CONTAINER BLUE HDPE 56020S			
Food simulant: **Ethylic alcohol 95% V/V in aqueous solution**			
Contact condition: **10 days at 60°C**			
Measured unit: **mg/dm²**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Regulation 10/2011/EC)
3.0	3.7	1.4	10 (+ 2)
4.4			
3.8			

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CONTAINER BLUE HDPE 56020S Food simulant: **Rectified olive oil** Contact condition: **10 days at 60°C** Measured unit: **mg/dm²**						
measured value	**average value**	**Extended uncertainty**	**To be subtracted from replications average if >2**	**Replications average – volatiles average**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
<1	<1	---	<1	<1	---	10 (+ 3)
<1						
<1						

2) QUANTITATIVE DETERMINATION OF PRIMARY AROMATIC AMINES: METHOD L.00.00-6 (LMBG § 35)

CONTAINER BLUE HDPE 56020S Food Simulant: **Acetic acid in aqueous solution 3% w/v** Contact condition: **10 days at 60°C**			
Measured value	**Average value**	**Standard deviation**	**Limit value** (according to Regulation 10/2011/EC)
<0.002 mg/Kg	<0.002 mg/Kg	--	0.01 mg/Kg
<0.002 mg/Kg			

3) SPECIFIC MIGRATION OF BA, CO, MN, ZN, CU, FE, LI

CONTAINER BLUE HDPE 56020S Food simulant: **Acetic acid in aqueous solution 3% w/v** Contact condition: **10 days at 60°C** Measured unit: **mg/kg**			
Metals	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
Ba	< 0.02	-	1
Co	< 0.02	-	0.05
Mn	< 0.02	-	0.6
Zn	< 1	-	25
Cu	< 1	-	5
Fe	< 1	-	48
Li	< 0.02	-	0.6

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Data: *Date:* 28/02/2013

CONTAINER BLUE HDPE 56020S			
Food simulant: **Ethylic alcohol 95% V/V in aqueous solution**			
Contact condition: **10 days at 60°C**			
Measured unit: **mg/kg**			
Metals	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
Ba	< 0.02	-	1
Co	< 0.02	-	0.05
Mn	< 0.02	-	0.6
Zn	< 1	-	25
Cu	< 1	-	5
Fe	< 1	-	48
Li	< 0.02	-	0.6

CONTAINER BLUE HDPE 56020S			
Food simulant: **Rectified olive oil**			
Contact condition: **10 days at 60°C**			
Measured unit: **mg/kg**			
Metals	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
Ba	< 0.02	-	1
Co	< 0.02	-	0.05
Mn	< 0.02	-	0.6
Zn	< 1	-	25
Cu	< 1	-	5
Fe	< 1	-	48
Li	< 0.02	-	0.6

4) SPECIFIC MIGRATION OF 1-HEXENE

CONTAINER BLUE HDPE 56020S			
Food Simulant: **Acetic acid 3% w/v in aqueous solution**			
Contact condition: **10 days at 60°C**			
Measured unit: **mg/kg**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
< 1	< 1	---	3
< 1			
< 1			

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CONTAINER BLUE HDPE 56020S			
Food Simulant: **Ethylic alcohol 95% V/V in aqueous solution**			
Contact condition: **10 days at 60 °C**			
units of measurement: **mg/kg**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
< 1	< 1	---	3
< 1			
< 1			

CONTAINER BLUE HDPE 56020S			
Food Simulant: **Rectified olive oil**			
Contact condition: **10 days at 60 °C**			
Measured unit: **mg/kg**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
< 1	< 1	---	3
< 1			
< 1			

5) DETERMINATION OF THE SPECIFIC MIGRATION OF OCTADECYL 3-(3,5-DI-TERT-BUTYL-4-HYDROXYPHENYL)PROPIONATE (CAS 2082-79-3)

CONTAINER BLUE HDPE 56020S			
Food Simulant: **Acetic acid 3% w/v in aqueous solution**			
Contact condition: **10 days at 60°C**			
Measured unit: **mg/kg**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
< 1	< 1	---	6
< 1			
< 1			

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CSI CERTIFICAZIONE E TESTING

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Data: *Date:* 28/02/2013

CONTAINER BLUE HDPE 56020S			
Food Simulant: **Ethylic alcohol 95% V/V in aqueous solution**			
Contact condition: **10 days at 60 °C**			
units of measurement: **mg/kg**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
< 1	< 1	---	6
< 1			
< 1			

CONTAINER BLUE HDPE 56020S			
Food Simulant: **Rectified olive oil**			
Contact condition: **10 days at 60 °C**			
Measured unit: **mg/kg**			
Measured value	**Average value**	**Extended uncertainty**	**Limit value** (according to Reg.10/2011)
< 1	< 1	---	6
< 1			
< 1			

CONCLUSIONS

In the chosen test condition the sample **CONTAINER BLUE HDPE 56020S** is suitable to be used in contact with acidic, alcoholic (till 95%) and oily or fatty foodstuffs for which stimulants A, B, C, D1 and D2 are used.

The sample tested by this Laboratory are therefore suitable to come in contact with foodstuff mentioned above on condition that they have been produced employing the monomers, additives and technical support agents according to in force legislation, specific migrations are respected and they do not induce any organoleptic modification on foodstuff.

Date
28/02/2013

Division Head
Alberto Taffurelli

Managing Director
Pasqualino Cau

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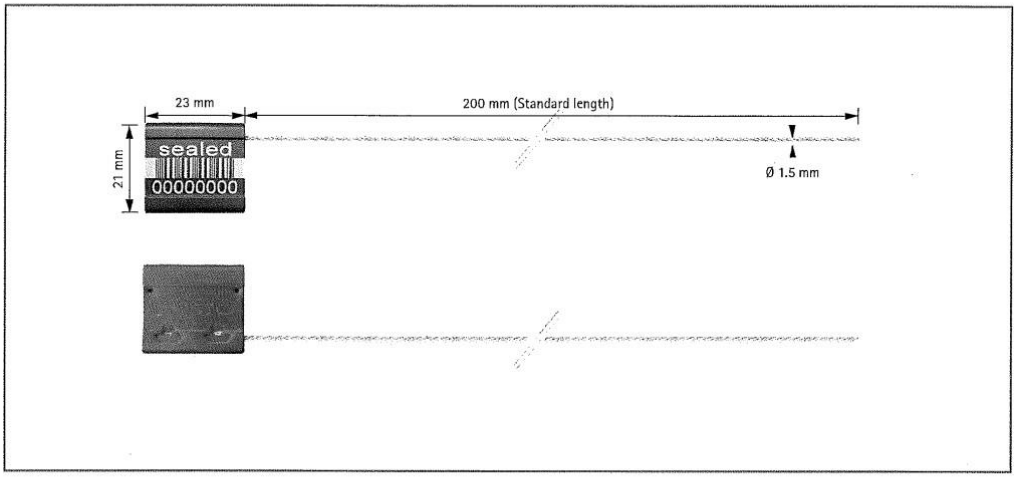
Anti-tampering seals

External seals for drums

UNISTO

Unisto Metalo 15



Destructive Tests (ISO/IEC PAS 17712)

Tensile: Above 3.0 kN
Shear: Below 227 kg-f
Bend: Above 501 Cycles (Flexible Seal)
Impact (low temperature): Below 27.12 J
Impact (high temperature): Below 27.12 J

Identifications Outer Casing

Specification: Laser Marked or Engraved
Logo/Abbreviations: 1 colour
Serial Numbers: Max. 7 digits Alphanumeric or Barcode

Material

Seal Casing: Aluminium
Cable: Galvanised Air Craft Cable
Locking Mechanism (Inter-locking Roller): Heat-treated Carbon Steel
Locking Mechanism (Tension Spring): Heat-treated High Tensile Steel

Packaging

Packing: 10 sequentially Seals bundled with Rubber Band 100 sequentially Bundles per Carton
Quantity: 1'000 Seals per Carton
Carton Dimensions: L 480 mm x W 260 mm x H 160 mm
Carton Weight: Approximate 10,14 kg

Dimensions

Seal Casing: L 23.0 mm x W 21.0 mm x T 7.0 mm
Cable: OD 1.5 mm x L 200 mm (Standard length)
Locking Mechanism (Inter-locking Roller): OD 7.2 mm x T 1.8 mm
Locking Mechanism (Tension Spring): OD 2.2 mm x L 8.0 mm x 9 Coils

Others

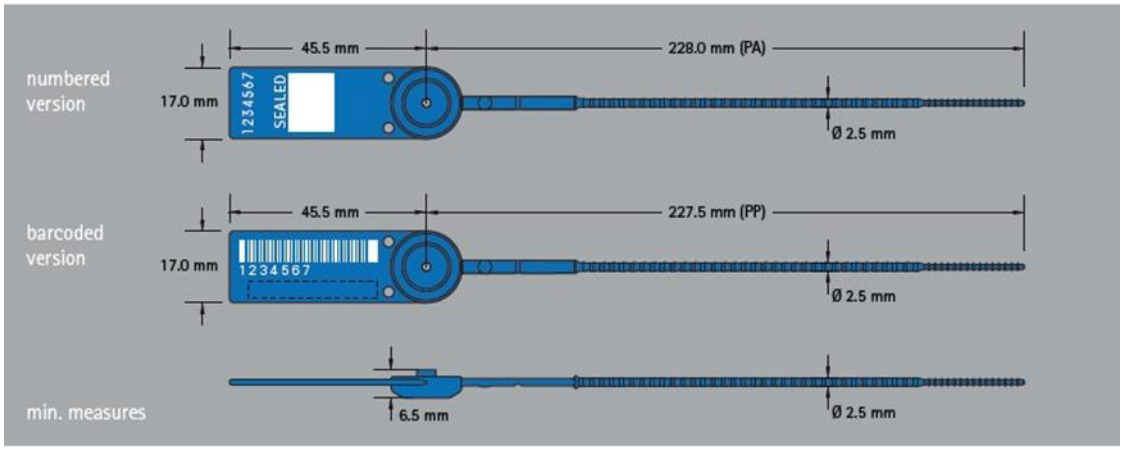
Colours: Blue, Green, Orange, Yellow, Red, White (Special Colours on request)

ISO 9001:2000, ISO/PAS 17712:2006 certified

Internal seals for PE bags

Unisto Medio

UNISTO



Technical Data Version Polyamide (PA)

Materials
Ribbon/housing: polyamide (PA)
Disc: polyamide (PA)
Locking mechanism: stainless spring steel

Tensile strength (loop), Unisto standard
Approx. 24 kg

Numbering
7 digits

Barcoding
Interleaved 2/5 or barcode 128

Customer name/logo
Foil printed or digital printing

Colours – numbered or digital printing version
Dark blue, dark green, red, grey, yellow, white, black

Other colours available on request

Packing
Mats of 10 pieces, box of 1000 seals
37.0 x 20.3 x 15.0 cm (0.012 m³), approx. 3.4 kg

Technical Data Version Polypropylene (PP)

Materials
Ribbon/housing: polypropylene (PP)
Disc: polypropylene (PP)
Locking mechanism: stainless spring steel

Tensile strength (loop), Unisto standard
Ca. 15 kg

Numbering
7 digits

Barcode
Interleaved 2/5 or barcode 128

Customer name/logo
Foil printed or digital printing

Colours – numbered version
Dark blue, dark green, red, grey, yellow, white, black

Other colours available on request

Colours – Barcode directly laser marked
White, yellow, apricot, pink, purple, grey, light brown

Packing
Mats of 10 pieces, box of 1000 seals
37.0 x 20.3 x 15.0 cm (0.012 m³), approx. 2.8 kg

ISO 9001, ISO 14001, OHSAS 18001 certified

Labeling

Label used for the packaging of the final API

Label used for the packaging of the final API only for US market

Ogliari srl	DICHIARAZIONE DI CONFORMITA'	DC01 Rev. 8 Genn 2017 Pag. 1 di 4

Doc. Nr.	Date:	Batch Nr.

To: CAMBREX PROFARMACO MILANO SRL
VIA CURIEL, 34
20067 PAULLO (MI)

Declaration of compliance

The undersigned: Osvaldo Ogliari
Acting as : Economic Operator
Representing the Company : **Ogliari S.r.l.**
Address: Viale Risorgimento 23 I-26017 Trescore Cremasco (CR),
Operator's activity in Italy: manufacturer of the primary packaging below:

Code	Description	Q.ty	Production date

CONFIRMS

That the products concerned comply with the provisions of the European Community to regulate the placing on the market, according to mandatory laws:
-Directive 94/62/EC (as amended) in conjunction with EN 13427: (Requirements for the use of European Standards in the field of packaging and packaging waste) as stated in below:

#1	**Manufacturing and Composition**	SI / NO/ NA (non applic.)
1.1	Prevention of use of resources (EN13428)	SI
1.2	Heavy metals <100ppm	SI
1.3	Content of dangerous substances (EN 13695-2)	SI
#2	**Reuse (EN 13429)** Not requested (see note in below)	NA
#3	**Recovery**	
3.1	Material recycling after use (EN13430)	SI
3.2	Energetic recovery (thermal) (EN 13431)	SI
3.3	Organic recovery for biodegradation (EN13432)	NO

Note: conformity with EN 13427 requires the affirmative answer to the following sections: 1.1, 1.2, 1.3 and, at a minimum, at least one of sections 3.1, 3.2, 3.3. In addition, if the customer makes a request for re-use, also section 2 is applicable.

Conformity for contact with food substances (EC)

Ogliari Srl confirms that the products covered by this Declaration, intended to come into contact with food substances, comply with the mandatory laws, regulations and EC Directives as below:
Regulation 1935/2004/EC, as amended, applicable to plastics
Regulation 2023/2006/EC (GMP), as amended, applies to plastic materials.
Regulation 10/2011/EC (PIM) and subsequent amendments (last update 174/2015/CE), applicable to plastics.
Monomers and additives used in the manufacture of these products, are listed on the EU list of authorized substances to regulation 10/2011/CE and subsequent modifications. The regulation 10/2011/EC quantifies in 10 mg/dm2 maximum global migration (OML) from food products in contact with food.
Ogliari Srl regularly check compliance with those limits by performing chemical analyses of migration according to the above at accredited laboratories.

National Laws:

Italy:These products are in accordance with the provisions in the "Ministerial Decree 3/21/1973" modified the 4/26/1993: DM No. 220 as amended (last updated: Ministerial Decree of 2/16/2011).
United States these products meet the FDA requirements contained in the Federal Code, Regulation 21 CFR 177.1520 (c) (3) (i) and (c) at 3.2.
These products may also contain adjuvants, substances which are also approved the manufacture of articles coming into direct contact with food. Materials used in this product are in accordance with the requirements of respective regulations 21 CFR 177.1520 FDA (b).

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The ingredients listed in annex II to Regulation (EU) no 1169/2011, are not used in the formulation and manufacture of these products. However, this product has not been tested specifically for these substances.

Pharmaceutical and biomedical use

These products comply with paragraph 3.1.3 EUROPEAN PHARMACOPOEIA and USP paragraph 661..

Latex

No material containing latex and/or natural rubber are used in the manufacturing, handling and packaging processes of this product.

Animal materials (BSE/TSE)

These products do not contain raw materials of animal origin in accordance with Regulation 1069/EC and 2009/142/EC 2011/in addition to the "explanatory note EMEA/410/01, rev. 3 about the BSE/TSE ("mad cow disease ")

Epoxy derivates

The BADGE, BFDGE or NOGE are not intentionally added to these products as set forth by Regulation EC/1895/2005, on the use of certain epoxy derivatives in materials and articles intended to come into contact with foodstuffs as plasticizers, additives or raw materials.

Nanomaterials (defined as natural materials, incidental or constructed, containing particles in the free state, aggregate or conurbation, and where at least 50% of the particles in numerical size distribution, one or more external dimensions is in the range of 1 nm size-100 nm) are not used in the manufacture and/or the formulation of these products. However, these products have not been tested for these substances.

Other chemicals the chemicals listed below are not used in the manufacture or formulation of these products, and therefore are not present.

However, these products have not been tested for these chemical substances:

2-(2H-1, 2, 3-Benzotriazol-2-yl)-4,6-di-tert-butylphenol; (Benzotriazole); CAS# 3846-71-7;
2,4,4'-trichloro-2'-hydroxydiphenyl ether; (Triclosan); CAS# 3380-34-5;
2-mercaptobenzothiazole; MBT; CAS# 149-30-4;
Acroleina; (propenal); (CAS# 107-02-8);
Acrylamide; CAS# 79-06-1;
Aromatic Amine ;
Asbestos;
Azo colorants and e pigments;
Hydrocarburi poliaromatic - PAHs:
1,2-dihydro-acenaphthene; (CAS# 83-32-9);
9H-Fluorene; (CAS# 86-73-7);
Acenaphthylene; (CAS# 208-96-8);
Anthracene; (CAS# 120-12-7);
Benz(a)anthracene; (CAS# 56-55-3);
Benzo(a)pyrene; (CAS# 50-32-8);
Benzo(b)fluoranthene; (CAS# 205-99-2);
Benzo(e)pyrene; (CAS# 192-97-2);
Benzo(ghi)perylene; (CAS# 191-24-2);
Benzo(j)fluoranthene; (CAS# 205-82-3);
Benzo(k)fluoranthene; (CAS# 207-08-9);
Chrysene; (CAS# 218-01-9);
Dibenz(a,h)anthracene; (CAS# 53-70-3);
Fluoranthene; (CAS# 206-44-0);
Formaldeyde; (CAS#50-00-0;
Indeno(1,2,3-cd)pyrene; (CAS# 193-39-5);
Naphthalene; (CAS# 91-20-3);
Phenanthrene; (CAS# 85-01-8);
Pyrene; (CAS# 129-00-0);
Benzophenone; CAS RN 119-61-9;
Bisphenol A; (BPA); CAS# 80-05-7;
Bisphenol A diglycidyl ether; (BADGE); CAS# 1675-54-3;

Bisphenol F diglycidyl ether; BFDGE; CAS# 2095-03-6;
Butylated hydroxyanisole; (BHA); CAS# 121-00-6 & 25013-16-5;
Butylated hydroxytoluene; (BHT); CAS# 128-37-0
Chlorinated paraffina;
Acido Cianurico; (Isocyanuric Acid or CYA); CAS# 108-80-5;
Dimethyl fumarato; (DMF); CAS# 624-49-7;
Dioxins;
Epichlorohydrina; (ECH); CAS# 106-89-8;
Fluorocarboni;
Fluorotelomeri
Formaldehyde; CAS# 50-00-0;
Halogenated Flame Retardants
Melamine; (1,3,5-Triazine-2,4,6-triamine); CAS# 108-78-1;
Nonylphenol; CAS# 25154-52-3;
Nonylphenol ethoxylates;
Novolac glycidyl ether;
Organotin compounds;
Perfluorochemicals; (PFCs);
Perfluorooctane sulfonate; (PFOS); CAS# 1763-23-1;
Perfluorooctanoic acid; (PFOA); CAS# 335-67-1;
Polybrominated biphenyls; (PBBs);
Polybrominated diphenyl ethers; (PDBEs);
Polybrominated terphenyls; (PBTs);
Polychlorinated biphenyls; (PCBs);
Polychlorinated naphthalenes; (PCNs);
Polychlorinated terphenyls; (PCTs);
Polystyrene;
Polyvinyl chloride; (PVC); CAS# 9002-86-2;
Radioactive substances;
Radon; CAS# 10043-92-2;
Styrene monomer; CAS# 100-42-5;
Sulphur dioxide; CAS# 7446-09-5;
Tin oxide (SnO2); (Cassiterite); CAS# 8062-08-6;
Tris-nonylphenol phosphite; (TNPP); CAS# 26523-78-4;
Vinyl chloride; CAS# 75-01-4;
Wolframite; Tungsten (W); CAS# 1332-08-7;

Phthalates

Phthalates are not used in the manufacture or formulation of these products. However, specific analyses were not performed

REACh SVHC substances

this product does not contain any chemical substances included in annex XIV (candidate to be Very High Concern Substances (last updated Jan. 2017), above the threshold of 0.1% as indicated in REACH (Article 57, regulation 1907/2006) determined through the non-use of the substance, the mass balance calculation and/or specific tests. The updated list of all the SVHC can be found at the link to the ECHA website follows:
http://echa.europa.eu/web/guest/candidate-list-tablePage

Conformity to the order and process verifications

Ogliari Srl confirms that the products covered by this Declaration are in accordance with the terms of delivery and inspected according to the applicable procedures laid down by its Quality Management System, ISO 9001: 2008 certified.
Ogliari Srl has realized the items described above in accordance with technical standards and regulations. All documentation in support of the certificate of compliance is available for the control authorities.

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Disclaimer:

The above information is accurate and reliable to the best of our knowledge, and updated to the date of issue of the certificate. In any case, Ogliari Srl assumes no responsibility for completeness of such information, which in some cases relys with certificate issued from our suppliers.

It is under the sole Customer responsibility to check and verify the products so that they meet requirements and therefore is suitable for use that the customer intends to make.

In particular, it is under the client's responsibility to ensure that the product comply to its intended use and in compliance with the legal requirements of the country where it wishes to sell them.

OGLIARI S.R.L. MAKES NO WARRANTIES, EXPRESS OR IMPLIED (INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE), UNLESS THE SAME ARE NOT EXPRESSLY AGREED UPON BETWEEN THE PARTIES TO A SPECIFIC CONTRACT.

This declaration is valid until revocation or modification. If the articles in question are legal or technical changes, Ogliari Srl shall provide for the release of a new declaration.

Ogliari SRL
Osvaldo Ogliari
Economic Operator

Date:

2.1.S.7 Stability

Stability summary and conclusions

PRC-Ticinum Lab in alternative stability testing laboratory (external). The analytical methods used to perform the Long-term stability studies have been transferred to PRC TICINUM LAB according to a specific procedure (PRC 01/13/PF, Analytical technology transfer). Cambrex Profarmaco Milano is responsible for sending the samples packaged as defined and for handling and presenting the analytical data obtained from PRC TICINUM LAB.

Stability specifications

Cysteamine bitartrate is analysed according to the stability specifications given below and were used to test the product during the Long-term stability and the Accelerated stability studies. The main potential degradation impurity is cystamine. This impurity is already included in the release specification of the final active ingredient and can be easily detected and quantified by volumetric titration. The test methods reported in the stability specification refer to those used for the release of the final active ingredient.

TEST	LIMITS	N°. Ed. Rev
Description	White crystalline powder	1.0601R
Loss on drying	NMT 0.5%	7.0601R
Assay by titration	97.0 – 102.0% (on dried basis)	9.0601R
Free Tartaric Acid	NMT 1.0%	10.0601
Cystamine (*) Content	NMT 2.0%	11.0701R

(*) known degradation impurities.

The Long-term stability study is conducted for 12 months. If after this time the product is stable, the retest date can be fixed in 12 months. On the contrary, if the product is not stable the expiry date depends on the degradation trend of the product. The Accelerated stability study is conducted for 6 months but can be extended if requested.

For stability studies, the product is maintained in a similar packaging of the finished product. This means that the samples are stored in the same type of bags and closures. The bags are then packaged into small plastic drums. For new products, the first three lots manufactured are put under Accelerated stability and Long-term stability. As per Cambrex Profarmaco Milano' stability protocol, every year, only one batch (as representative of commercial production every year), is added to the Long-term stability study unless no production is done. The API lot No. 860202 that was used for manufacturing API was not put under stability study.

Refrigerated Long-term stability studies

Refrigerated Long-term stability studies of cysteamine bitartrate are on-going on the following batches:

Batches	Batch size (Kg)	Date of manufacture
812122	275	12/2018
812324	267	12/2018
812526	294	12/2018

The lots were stored under the following conditions:

REFRIGERATED LONG TERM STABILITY (LTS)
Temperature: 5°C ± 3°C
Relative humidity: -

Conclusions of the Long-term stability study

The refrigerated Lon- term stability data generated until now according to the ICH guidelines, show that no significant degradation occurs after 9 months.

Therefore,

Cambrex Profarmaco Milano S.r.l. have assigned to cysteamine bitartrate a retest period under refrigerated conditions of **9 months.**

The Long-term stability data are provided in the tables below.

Cysteamine bitartrate: Long-term stability study data

Storage conditions: 5 ± 3 °C Type of packaging: Alluminio NON sott ovuot o Duration of the study: 2 years	Batch number: 812122 Manufacturing date: 12/12/2018 Stability study start: 20/12/2018

Test	Description	Release
1	Description	004-001
2	Loss on drying	004-001
3	Assay	004-001
4	Cystamine content	004-001

	Months	T0	1M	3M	6M	9M	12M	18M	24M
Test	**Limits Date:**	12-2018	1-2019	3-2019	6-2019	9-2019	12-2019	6-2020	12-2020
1	White crystalline powder	Complies	Complies	Complies	Complies	Complies			
2	NMT 0.5%	0.1	0.1	0.2	0.2	0.2			
3	By titration (on dried basis) 97.0-102.0%	98.9	99.6	99.6	98.0	99.1			
4	NMT 2.0%	1.1	0.7	0.7	1.2	1.1			

Cysteamine bitartrate: Long-term stability study data

Storage conditions: 5 ± 3 °C Type of packaging: Alluminio NON sottovuoto Duration of the study: 2 years	Batch number: 812324 Manufacturing date: 12/12/2018 Stability study start: 20/12/2018

Test	Description	Release
1	Description	004-001
2	Loss on drying	004-001
3	Assay	004-001
4	Cystamine content	004-001

	Months	T0	1M	3M	6M	9M	12M	18M	24M
Test	**Limits Date:**	12-2018	1-2019	3-2019	6-2019	9-2019	12-2019	6-2020	12-2020
1	White crystalline powder	Complies	Complies	Complies	Complies	Complies			
2	NMT 0.5%	0.1	0.1	0.2	0.2	0.4			
3	By titration (on dried basis) 97.0-102.0%	99.2	99.5	99.5	97.7	99.0			
4	NMT 2.0%	0.4	0.6	0.7	1.7	1.2			

Cysteamine bitartrate: Long-term stability study data

Storage conditions: 5 ± 3 °C Type of packaging: Alluminio NON sottovuoto Duration of the study: 2 years	Batch number: 812526 Manufacturing date: 13/12/2018 Stability study start: 20/12/2018

Test	Description	Release
1	Description	004-001
2	Loss on drying	004-001
3	Assay	004-001
4	Cystamine content	004-001

	Months	T0	1M	3M	6M	9M	12M	18M	24M
Test	**Limits Date:**	12-2018	1-2019	3-2019	6-2019	9-2019	12-2019	6-2020	12-2020
1	White crystalline powder	Complies	Complies	Complies	Complies	Complies			
2	NMT 0.5%	0.0	0.1	0.1	0.1	0.1			
3	By titration (on dried basis) 97.0-102.0%	99.1	99.7	99.4	97.9	99.0			
4	NMT 2.0%	0.5	0.5	0.7	1.9	1.1			

Accelerated stability studies

Accelerated stability studies of cysteamine bitartrate have been conducted on the following batches:

Batches	Batch size (Kg)	Date of manufacture
812122	275	12/2018
812324	267	12/2018
812526	294	12/2018

These lots were stored under the following conditions:

ACCELERATED STABILITY (AS)
Temperature: 25°C ± 2°C
Relative humidity: 60% ± 5%

Conclusions of the accelerated stability study

The accelerated stability data generated until now according to the ICH guidelines show that significant degradation occurs after 6 months.

The Accelerated stability data are provided in the tables below.

Cysteamine bitartrate: Accelerated stability study data

Storage conditions: 25 ± 2 °C Relative humidity: 60% ± 5% Type of packaging: Alluminio NON sottovuoto Duration of the study: 6 months	Batch number: 812122 Manufacturing date: 12/12/2018 Stability study start: 20/12/2018

Test	Description	Release
1	Description	004-001
2	Loss on drying	004-001
3	Assay	004-001
4	Cystamine content	004-001

	Months	T0	1M	3M	6M				
Test	**Limits Date:**	12-2018	1-2019	3-2019	6-2019				
1	White crystalline powder	Complies	Complies	Complies	Complies				
2	NMT 0.5%	0.1	0.1	0.2	0.1				
3	By titration (on dried basis) 97.0-102.0%	98.9	99.3	98.5	97.2				
4	NMT 2.0%	1.1	0.7	1.6	2.5				

Cysteamine bitartrate: Accelerated stability study data

Storage conditions: 25 ± 2 °C Relative humidity: 60% ± 5% Type of packaging: Alluminio NON sottovuoto Duration of the study: 6 months	Batch number: 812324 Manufacturing date: 12/12/2018 Stability study start: 20/12/2018

Test	**Description**	**Release**
1	Description	004-001
2	Loss on drying	004-001
3	Assay	004-001
4	Cystamine content	004-001

	Months	**T0**	**1M**	**3M**	**6M**				
Test	**Limits** **Date:**	12-2018	1-2019	3-2019	6-2019				
1	White crystalline powder	Complies	Complies	Complies	Complies				
2	NMT 0.5%	0.1	0.1	0.3	0.1				
3	By titration (on dried basis) 97.0-102.0%	99.2	99.7	99.7	96.9				
4	NMT 2.0%	0.4	0.6	0.5	3.0				

Cysteamine bitartrate: Accelerated stability study data

Storage conditions: 25 ± 2 °C Relative humidity: 60% ± 5% Type of packaging: Alluminio NON sottovuoto Duration of the study: 6 months	Batch number: 812526 Manufacturing date: 13/12/2018 Stability study start: 20/12/2018

Test	**Description**	**Release**
1	Description	004-001
2	Loss on drying	004-001
3	Assay	004-001
4	Cystamine content	004-001

	Months	**T0**	**1M**	**3M**	**6M**				
Test	**Limits** **Date:**	12-2018	1-2019	3-2019	6-2019				
1	White crystalline powder	Complies	Complies	Complies	Complies				
2	NMT 0.5%	0.0	0.1	0.2	0.1				
3	By titration (on dried basis) 97.0-102.0%	99.1	99.6	98.4	97.2				
4	NMT 2.0%	0.5	0.6	1.8	2.4				

2.1.P Investigational medicinal product under test

2.1.P.1 Description and composition of the investigational medicinal product

An intravenous (IV) formulation of cysteamine bitartrate, (containing 500 mg/2.5 mL) was developed to use in REMAP-CAP clinical trial. The IV formulation was manufactured using the cysteamine bitartrate API (batch# 860202) that was obtained from Cambrex Profarmaco Milano S.r.l.

The IV formulation was developed as IV is the preferred route for administering cysteamine bitartrate for severe acutely ill patients hospitalized in the intensive care unit. It is intended that cysteamine bitartrate will be given as IV bolus infusion in the REMAP-CAP trial, and the composition of each vial is provided in the table below.

IV cysteamine bitartrate (500 mg/2.5 mL) (2 mL vial with 2.5 mL fill volume)		
Material	**Function**	**IV cysteamine bitartrate**
Cysteamine bitartrate	Active ingredient	500 mg/2.5 mL fill volume (200 mg/mL)
Water for Irrigation (WFI) Ph. Eur. (contained in bottles)	Sparged WFI used for preparation of the 10 M NaOH and cysteamine bitartrate solution.	-
10 M Sodium hydroxide (NaOH) solution, Ph.Eur, BP, FCC, JP, NF, E524 (CAS # 1310-73-2)	To adjust pH of cysteamine bitartrate solution to target pH of 5.5 (limits pH 5.0-6.0)	-
Nitrogen	Overlay of vials / purging of bulk solution	-

2.1.P.2 Pharmaceutical development

Oral cysteamine bitartrate has been licensed for over 25 years with safety data collected over 30 years. This is the first IV formulation of cysteamine bitartrate developed to be used in the REMAP-CAP clinical trial for COVID associated pneumonia. Cysteamine bitartrate, 200 mg/mL is a sterile solution in a sealed 2 mL vial with a fill volume of 2.5 mL.

2.1.P.2.1 Manufacturing process development

Formulation strategy: Cysteamine bitartrate is a non-cytotoxic, small molecule with good aqueous solubility (>100 mg/mL). The parenteral formation of cysteamine bitartrate was developed as a simple aqueous solution for frozen storage with minimal/no additional excipients.

Formulation development study

PH SOLUTION STABILITY ASSESSMENT

The manufacturer undertook a pH screening exercise to identify an appropriate pH for optimum cysteamine bitartrate solution stability. The effect of pH on solution stability comprised the first aspect of the formulation screening exercise.

The stability of nominal 200 mg/mL cysteamine bitartrate solution was assessed over a range of pH's (5.5, 6.5 and 7.5). Small volumes (40 mL) were prepared (materials and formulations shown below in table), sealed in Type I glass vials and set down on short term stability at three storage conditions (-20°C, 2-8°C and 25°C/60% RH). The vials were assayed for cysteamine content and purity at T = 0, T = 6 hours and T = 24 hours. The appearance and pH were also recorded. To reduce the oxygen levels in the WFI, it was sparged with nitrogen before use. After identifying the stable formulation, the formulation was transferred to manufacturing GMP clinical batch.

The materials used during the pH solution stability assessment are given in **Table** below.

Table: Materials

Material	Supplier	Lot
Cysteamine bitartrate	Cambrex	002155CYSFA
WFI	Baxter	20BIOBAIB
10M Sodium hydroxide	Merck	B1359182727

The formulations (prepared at a 40 mL scale) and stability conditions are provided in the Tables below.

Table: Formulation details

Formulation	[Cysteamine bitartrate] (mg/mL)	Target pH
F1	200	5.5
F2	200	6.5
F3	200	7.5

Storage condition	Time-point		
	T = 0	T = 6 hours	T = 24 hours
-20°C	APH	APH	APH
2-8°C		APH	APH
25°C/60% RH		APH	APH

A=Appearance of solution; P=pH; H =HPLC

Results

Appearance and pH results

There was no significant change in appearance or pH for Formulation 1, 2 and 3 at any of the storage conditions throughout the pH solution stability study.

Assay results

Assay results for Formulation1: Assay (mg/mL)

Formulation/ storage	Prep 1 (mg/mL)	Prep2 (mg/mL)	Mean (mg/mL)	Theoretical[1] (%)	Rec./T = 0 (%)[2]
T = 0	192.644	190.592	191.618	95.8	-
T = 6 h, -20°C	189.208	192.240	190.724	95.4	99.5
T = 6 h, 2-8°C	190.362	192.119	191.240	95.6	99.8
T = 6 h, 25°C/60% RH	188.149	185.321	186.735	93.4	97.5
T = 24 h, -20°C	187.944	193.378	190.661	95.3	99.5
T = 24 h, 2-8°C	189.135	189.324	189.230	94.6	98.8
T = 24 h, 25°C/60%RH	185.604	181.125	183.365	91.7	95.7

[1]Calculated as percentage of theoretical 200 mg/mL; [2]Calculated as a percentage of recovery v T = 0.

No significant loss in % Recovery was noted over the 24 h stability period for Formulation 1 when stored at -20°C. There is a slight drop in % Recovery for formulation 1 when stored at conditions, 2-8°C and 25°C/60% RH. The % Recovery loss is more significant at the accelerated condition, 25°C/60% RH.

Assay results for Formulation2: Assay (mg/mL)

Storage	Prep 1 (mg/mL)	Prep2 (mg/mL)	Mean (mg/mL)	Theoretical (%)[1]	Rec./T = 0 (%)[2]
T = 0	187.779	187.633	187.706	93.9	-
T = 6 h, -20°C	181.677	183.746	182.712	91.4	97.3
T = 6 h, 2-8°C	179.223	165.852	172.537	86.3	91.9
T = 6 h, 25°C/60% RH	176.753	172.846	174.799	87.4	93.1
T = 24 h, -20°C	185.296	184.307	184.801	92.4	98.5
T = 24 h, 2-8°C	181.280	175.690	178.485	89.2	95.I
T = 24 h, 25°C/60% RH	157.975	159.414	158.695	79.3	84.5

[1]Calculated as percentage of theoretical 200 mg/mL; [2]Calculated as a percentage of recovery v T=O.

Slight loss in % Recovery for Formulation 2 over the 24hr stability period when stored at 20°C. There is a significant loss for samples stored at 2-8°C at the T = 6 h time point however, after

24 h the % Recovery increases. The initial loss potentially could be due to sample preparation as the sample area for the replicates between the samples at T = 6 h varies. There is a significant drop in % Recovery (>10%) over the 24 h period at 25°C/60% RH.

Assay results for Formulation3: Assay (mg/mL)

Storage	Prep 1 (mg/mL)	Prep2 (mg/mL)	Mean (mg/mL)	Theoretical (%)[1]	Rec.IT = 0 (%)[2]
T = 0	169.903	157.172	163.538	81.8	-
T = 6 h, -20°C	177.846	172.789	175.317	87.7	107.2
T = 6 h, 2-8°C	163.057	161.418	162.237	81.1	99.2
T = 6 h, 25°C/60% RH	132.848	156.177	144.512	72.3	88.4
T = 24 h, -20°C	173.892	149.443	161.668	80.8	98.9
T = 24 h, 2-8°C	164.630	136.752	150.691	75.3	92.1
T = 24 h, 25°C/60% RH	136.748	125.133	130.940	65.5	80.1

[1]Calculated as percentage of theoretical 200 mg/mL; [2]Calculated as a percentage of recovery v T=0.

Initial recovery (T = 0) for Formulation 3 is lower than expected (<90%) and the lowest recovery obtained when compared to the other two formulations. The % Recovery for the -20°C condition at T = 6 h increased however, at T = 24 h the recovery was comparable to T = 0. There is a significant loss in % Recovery for both 2-8°C and 25°C/60% RH conditions throughout the stability study.

Related substances

Formulation1; Related Substances (rel area%)

RRT	Time-point/storage						
	Initial (T = 0)	T = 6 h, -20°C	T = 24 h, -20°C	T = 6 h, 2-8°C	T = 24 h, 2-8°C	T = 6 h, 25°C/60% RH	T = 24 h, 25°C/60% RH
3.06	ND	ND	ND	ND	ND	ND	ND
3.38	ND	ND	ND	ND	ND	ND	ND
Cystamine (base)	3.04	3.70	4.64	4.17	5.05	5.77	8.22
Total	**3.0**	**3.7**	**4.6**	**4.2**	**5.1**	**5.7**	**8.2**

ND: Not Detected

There is a significant increase in cystamine (base) for all storage conditions over the 24 h stability study. The most significant increase in % rel area of Cystamine is obtained at the 25°C/60%RH storage condition.

Formulation2; Related Substances (rel area%)

RRT	Time-point/storage						
	Initial (T = 0)	**T = 6 h, -20°C**	**T = 24 h, -20°C**	**T = 6 h, 2-8°C**	**T = 24 h, 2-8°C**	**T = 6 h, 25°C/60% RH**	**T = 24 h, 25°C/60% RH**
3.06	ND	ND	ND	ND	ND	ND	ND
3.38	ND	ND	ND	ND	ND	ND	ND
Cystamine (base)	3.80	7.45	6.13	12.81	10.40	11.81	21.45
Total	**3.8**	**3.5**	**6.1**	**12.8**	**10.4**	**11.8**	**21.5**

There is a significant increase in cystamine (base) for all storage conditions over the 24 h stability study. There is a larger increase in cystamine obtained with Formulation 2 than what was obtained with Formulation 1 and the most significant increase in % rel area of cystamine was obtained at condition 25°C/60% RH.

Formulation3; Related Substances (rel area%)

RRT	Time-point/storage						
	Initial (T = 0)	**T = 6 h, -20°C**	**T = 24 h, -20°C**	**T = 6 h, 2-8°C**	**T = 24 h, 2-8°C**	**T = 6 h, 25°C/60% RH**	**T = 24 h, 25°C/60% RH**
3.06	ND	ND	ND	ND	ND	ND	ND
3.38	ND	ND	ND	ND	ND	ND	ND
Cystamine (base)	19.90	14.38	22.52	21.42	28.05	31.42	38.50
Total	**19.9**	**14.4**	**22.5**	**21.4**	**28.1**	**31.4**	**38.5**

There is a significant increase in cystamine (base) for all storage conditions over the 24 h stability study with the exception of T = 6 h for -20°C which sees a decrease in Cystamine. However, it has increased at T =2 4 h and is greater than the% rel area at T = 0. Formulation 3 sees the largest increase in cystamine in comparison to Formulation 1 and Formulation 2 with the most significant increase in % rel area obtained at condition 25°C/60% RH.

Conclusion

The pH of the three formulations remained stable throughout the stability study for all assessed storage conditions.

There is a clear trend of decreasing assay after 24 hours storage at 25°C/60% RH with increasing pH target for the formulation (F1 = 95.7%, F2 = 84.5%, F3 = 80.1%).

The related substances data shows that with increasing pH the total related substances, primarily cystamine (base), also increases (F1 = 8.2 % rel area, F2 = 21.5 % rel area, F3 = 38.5 % rel area).
Based on these findings a target pH of pH 5.5 was selected for the upcoming non-GMP technical batch as this formulation (F1) was the most stable with regards to assay and related substances.

Description of technical batch (Batch No: 001/NVB/20)

Small scale non-GMP technical batch (Batch No: 001/NVB/20) of IV cysteamine bitartrate was first manufactured in May 2020 using the formulation and processes as identified in preceding stages. A non-GMP batch size of 1400 mL active solution at 200 mg/mL cysteamine corresponding to 500 vials was manufactured. The formulation composition of the non-GMP technical batch, (Batch No: 001/NVB/20) is reported in the table below. The vials were labelled standard label of the IMP manufacturer and stored in the freezer at -15 to -25°C. The technical Batch Record (TBRs) was prepared to document the manufacture and support future technical transfer to GMP manufacturing.

Material description	Concentration (mg/mL)	Weight for 1400 mL batch
Cysteamine bitartrate (API lot number: 751111)	200	282 g*
Sodium hydroxide solution 10M	-	q.s. pH 5.5
Water for Irrigation (WFI)	-	q.s. 1400 mL

*no potency correction required.

The non-GMP was manufactured with the final formulation composition to support the developmental analytical work, analytical method validation, non-GMP stability testing and in preparation for GMP manufacture and validation of sterility testing.

Clinical batch (lot No. P04620)

Large scale GMP production of the IMP was manufactured on Dec 2020. A batch size of approximately 18,500 mL, corresponding to 7000 vials was manufactured for clinical trial use and also for supporting the GMP stability data. The formulation of the GMP clinical batch is provided below in **Section 2.1.P.3.2 (Batch formula)**. After manufacturing, the vials were stored in freezer at -15°C TO -25°C.

Method of preparation and administration of IV cysteamine bitartrate

IV cysteamine bitartrate 200 mg/mL should be reconstituted in 100 mL of 0.9% NaCl prior to administration. The stability and compatibility testing of the cysteamine bitartrate solution with the diluent and IV administration sets are provided in the **Stability Section 2.1.P.7**. The instructions for preparation and IV administration cysteamine bitartrate are summarised below and a full description for thawing process and instructions for administration are provided in the pharmacy guide version 3 dated 18 August 2021.

Instructions for IV administration of cysteamine bitartrate

- Cysteamine bitartrate 200 mg/mL is a concentrated solution and should be diluted in 0.9% NaCl prior to administration intravenously.
- Calculate the volume (mL) of cysteamine bitartrate required based on patient's estimated or actual body weight.
- Withdraw the required volume of cysteamine bitartrate using a needle and 1 mL or 5 mL syringe and add to a 100 mL 0.9% NaCl solution infusion bag.
- Invert the infusion bag 10 times to ensure homogenous mixture of the solution. Inspect the bag and only bags which are clear and free of visible particles can be infused.
- Attach the bag to the IV administration set and then set the rate to administer the entire infusion bag within 15 minutes.

2.1.P.2.2 Manufacturer(s)

Both non-GMP and GMP batch of IV cysteamine bitartrate was manufactured by:

~~**Albany Molecular Research Inc. (Glasgow) Limited [AMRI]**~~
Curia (Scotland) Limited
Todd Campus,
West of Scotland Science Park,
Glasgow G20 0XA,~~.~~
United Kingdom.

Albany Molecular Research Inc. (Glasgow) Limited changed its company name from AMRI to Curia (Scotland) Limited in July 2021. However, the address remained same. As the company changed its name during the project, AMRI and Curia (Scotland) are being mentioned interchangeably throughout the document.

Albany Molecular Research Inc. (Glasgow) Limited performed the developmental analytical works, In-Process Controls, In-use testing, stability testing, batch release, GMP QP release of the bulk IMP product and labelling and packaging of the vials. A copy of the manufacturer's authorization and GMP certificate of Albany Molecular Research Inc. (Glasgow) Limited is enclosed in **Appendix 3.1.A.1.**

Sterility testing was conducted by AMRI contractors:

Charles River Laboratories Ireland Limited
Carrentrilla, Ballina
Co. Mayo
Ireland
F26 A786

2.1.P.2.3 Batch formula

The batch size (**lot No. P04620**) of 7000 vials corresponding to 18,500 mL of cysteamine bitartrate solution was manufactured and filled in a 2 mL clear glass vials with a fill volume of 2.5 mL per vial. The batch formula is reported in the table below.

Material description	**Concentration (mg/mL)**	**Quantity required for GMP batch (18,500 mL)**
Cysteamine bitartrate	200	3775.5 g
Sodium hydroxide solution 10 M	-	800 g
Water for irrigation (WFI)	-	20368.5 g

2.1.P.2.4 Description of manufacturing process and process controls

This section summarises the manufacturing process of the IMP.

Drug product, Bulk Manufacturing

The API cysteamine bitartrate was dissolved in purged WFI and mixed with NaOH solution to attain a target pH for the IV cysteamine bitartrate solution. WFI was sparged for ≥30 minutes ahead of all manufacturing activities. Nitrogen was used to overlay vials and for purging bulk solution. Cysteamine bitartrate is oxygen sensitive, therefore headspace of material weighed/vessels/vials were blanketed with nitrogen during all compounding activities due to stability of product.

Calculations for preparing NaOH solution and cysteamine bitartrate solutions for bulk manufacturing are provided in the tables below.

Sodium hydroxide solution calculation: 10 M NaOH Solution. Density 1.33 g/mL

Material	Ingredient Item Master number	Quantity required	Quantity weighed
Sodium hydroxide - Ph.Eur, BP, FCC, JP,NF, E524 (CAS #1310-73-2)	GRMA0105	800 g	800 g
Water for irrigation (WFI in Bulk) Ph. Eur. (Contained in Bottles)	GRMA0042	2660.0 g	2660.02 g
Mole x Relative Molecular Mass = Mass RMM of Sodium hydroxide (NaOH) = 40.00 g/mol Mole = 10 10 mol x 40.00 g/mol = 400 g; 2 L x 400 g = 800 g			

Cysteamine bitartrate calculations: Density: 1.101 g/mL

Material	Ingredient Item Master number	API batch number	Quantity required	Quantity weighed
Cysteamine bitartrate (API)	GAPI0263	860202	3775.5 g	3775.5 g
Water for irrigation (WFI in Bulk) Ph. Eur. (Contained in Bottles)	GRMA0042		20368.5 g	20418.6**
Assay (by titration on dried basis) *: 98.0% (per API CoA) Concentration required: 200 mg/mL Batch volume required: 18500 mL API required: Concentration x volume: 200 mg/mL x 18500 mL = 3775510 mg = 3775.5 g Correction factor 98.0%				
Batch weight= volume x density = 18500 mL x 1.101 g / mL = 20368.5 g 70% Batch weight = 20368.5 g x 0.70 = 14258.0 g				
*Assay value used for correction factor **Target bulk weight was 20368.5 g, however the actual weight recorded after transferring solution to compounding vessel 2 was 20418.6**. Therefore, the target weight was overshot by 50.1 g (represents 0.2% overshot). Authorisation was given to proceed without further adjustment as this overage will not impact on the quality of the product. This issue was discussed with QA and the cause of the issue was found to relate to the way the solution was prepared. The initial dissolution weight should have been 70% of the target batch volume instead of the target batch weight and as a corrective action, this should be followed for the future manufacturing of the product to prevent recurrence of this issue. A note to file was prepared documenting this deviation and signed by QA.				

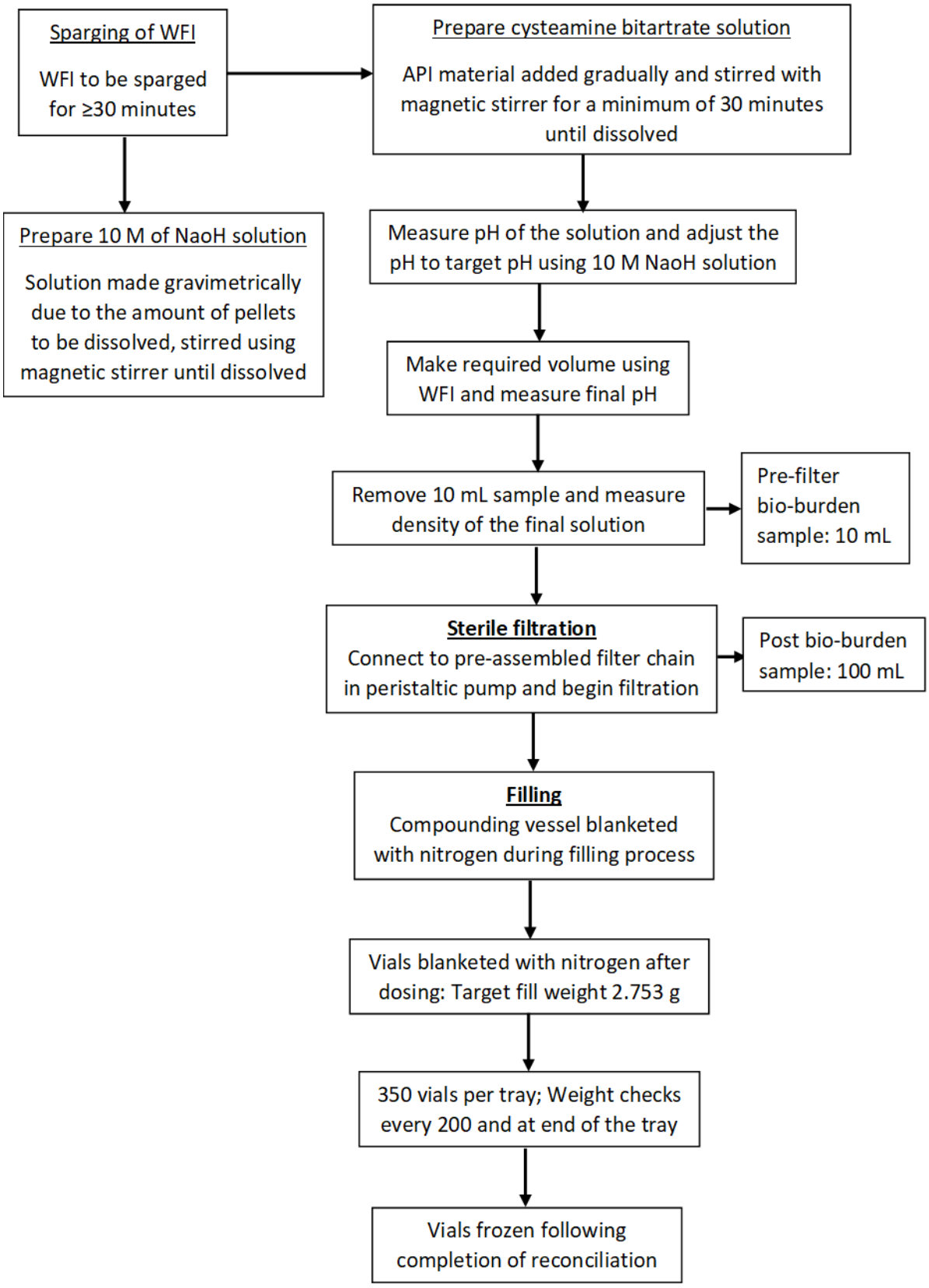
Batch configuration is as given in the table below:

Batch configuration	
VIAL SIZE AND TYPE	Vial – 2 mL clear (VC002-13C)
STOPPED SIZE AND TYPE	13 mm Injection Stopper Flurotec (New Generation) 4023/50 B2-40 Westar RS (WPS # 1012- 2737) INJ13TB3WSRS
OVERSEAL SIZE AND TYPE	13 mm Tear Off Overseal CETW13 WPS # 5920-2274
FILTER TYPE (PRE-FILTRATION)	Millipak 100 MPGL1GCL3 (0.22 µm)
FILTER TYPE (STERILE FILTRATION)	Millipak 60 PUPSIT System MIL0001L1807247 (0.22 µm)
HOLDING VESSEL / TUBING	20 L Jacketed Bottle with 3.2 mm bung assembly/1.6 mm filling line

The handling requirements of the materials are as follows:

Material description	Handling requirements
Cysteamine bitartrate	Hygroscopic, keep container sealed, store in desiccator.
Sodium hydroxide	Corrosive, wear appropriate PPE and use in fume hood.
WFI	Purge WFI with nitrogen prior to use

A flow chart of the IV cysteamine bitartrate manufacturing process is provided below



Drug product, sterile filtration and filling of vials

IMP solution was passed through two sterile filter, Millipak 60 (0.22 µm) and the headspace of holding vessel was blanketed with nitrogen throughout the filling process. After the sterile filtration, filtrate was filled by peristaltic pump, into 2 mL Type I glass vias (Schott). The vials were filled and purged with nitrogen after dosing and were closed with butyl rubber Flurotec coated stoppers (West) and secured with over-seals (West). Weight checks were carried out for every 200 vials and at the end of the tray. Crimps were checked at the end of every tray. If crimp filling failed, vials were passed out of the clean room for reconciliation.

Visual inspection

Vials were visually inspected. As the drug product is temperature sensitive, IMP was stored at -20 ± 5°C and visual inspection was carried out on dry ice on a box-by-box basis to minimize the time out of storage. Due to the limitations of inspecting frozen vials, a destructive test method was applied whereby 20 vials were thawed and inspected as liquid vials.

Naked primary containers were packed into black Corex boxes following visual inspection and identified using standard label text of Albany Molecular Research Inc. (Glasgow) Limited.

Premises, equipment, and materials

All manufacturing operations were carried out according to the current Good Manufacturing Practices. All product contact items including vials, glassware and peripherals will be sterilised by depyrogenation in the hot air oven at 250°C for 120 minutes after twice rinsing with WFI. Product contact tubing, stoppers and over-seals will be twice rinsed with WFI then sterilised by autoclaving for >15 minutes at 121°C then dried overnight in a drying oven. The cleanliness of premises and equipment was checked before each manufacturing operation. All operations followed approved standard operating procedures. Personnel wore suitable clothes.

2.1.P.2.5 Control of critical steps and intermediates

The following In-Process tests were carried out.

In-Process Controls

The following In-Process controls executed during the bulk manufacturing process.

Bioburden samples were taken from the bulk formulation (10 mL) and post pre-sterilisation filtration (100 mL). Both samples were tested as part of routine GMP batch manufacture. Using the bulk formulation, verification of the standard AMRI Glasgow bioburden approach was undertaken. Formulation was passed through a filter and growth promotion performed with two challenge organisms:

- *Staphylococcus aureus*
- *Candida albicans.*

Control	Phase/Test	Sample size	Storage	Specification criteria
Bioburden sampling	Pre-filtration bulk solution (Pre-bioburden reducing filtration)	10 mL sample/ Millipak 100 pre-filter.	Checked for appearance and stored at -20 °C prior to testing	<100 cfu/100 mL
Bioburden sampling	Pre-filtration bulk solution (Post bioburden reducing filtration)	100 mL sample		≤10 cfu/100 mL

Results: Samples passed bioburden testing.

ADSORPTIVE LOSSES ON FILTRATION

During GMP manufacture, the bulk solution was filter sterilised (0.22 µm pore size). Therefore, as part of formulation development work, a filtration assessment for cysteamine bitartrate drug product at a concentration of 200 mg/mL was carried out. Compatibility with the filter and possible loss of material by adsorption onto the filter membrane and housing was investigated. The useful in-house arrangement was to ensure that the ratio of filtered volume (mL) to total filter surface (cm^2) is ≥5.

Table: Batch details

Component	Concentration (mg/mL)
Cysteamine bitartrate	200
WFI	q.s. 400 mL
10M Sodium Hydroxide	q.s. pH 6.5

The formulation detailed in **Table** above was prepared at 400 mL scale.

A bulk solution (500 mL) was prepared at a selected pH of 6.5 pH (selected prior to completion of pH solution stability assessment). A known volume was passed, by peristaltic pump and platinum-cured silicone tubing through proprietary grade filter capsules of known surface area to assess adsorptive losses per cm^2 of filter surface area. The two filter membrane types which were assessed were Polyvinylidene fluoride (PVDF) and polyether sulfone (PES).

Ease of filtration, measured as the back pressure up-stream of the filter was assessed for each filter type. Cysteamine bitartrate concentration in the five successive early samples of the filtrate and the final bulk filtrate have been determined by HPLC. The pH of the pre-filter and final bulk solution has been measured. Typically, a pre-filtration sample is retained and analysed by HPLC along with the five successive samples of the filtrate. Unfortunately, in this case, a pre-filtration sample was not taken in error, this was only discovered once the sample had been passed through each of the filters.

The filter details and materials used are provided in the Table below.

Filter details

Description	Filter membrane	Filter housing	Supplier	Item no.	Lot no.
Mini Kleenpak	PES	Polypropylene/ polycarbonate	Pall	KAOZEBVPZS	IE9176
Millipak 20	PVDF	Polycarbonate	Millipore	MPGLO2GH2	C0AB89480

Table: Materials

Component	Concentration (mg/mL)	Supplier	Lot
Cysteamine bitartrate	200	Cambrex	751111
WFI	q.s.	Baxter	20B10BA1B
10 M Sodium hydroxide	q.s.	Merck	B1359182727

Table: Testing requirements

Test	Sample size	Method	Criteria
Appearance	N/A	Visual	Record results for information only
Cysteamine bitartrate Assay & Related substances	N/A	IMPD v01 of oral cysteamine bitartrate	

Experimental

Preparation of 200 mg/mL cysteamine bitartrate solution

The formulation detailed in **Table** above was prepared at 400 mL scale as per the following method:

Approximately 500 mL of WFI was sparged with nitrogen gas for 15 minutes and 80.0543 g of cysteamine bitartrate API was weighed into a glass beaker. Following this, 200 mL of nitrogen sparged WFI was measured and transferred to a 600 mL glass beaker containing a magnetic stirrer bar. The API was added to the 200 mL of the nitrogen sparged WFI whilst stirring until completely dissolved, dissolution took approximately 15 minutes.

The pH of the solution was measured, pH 3.38, and adjusted to pH 6.47 using approximately 35 mL of 10 M NaOH. Once the pH was adjusted, the solution was transferred to two 200 mL volumetric flasks and made to volume with the nitrogen sparged WFI. The flasks were inverted to mix and combined in the original compounding beaker.

Filtration of 200 mg/mL cysteamine bitartrate solution

The bulk was split into two 200 mL solutions to assess both filter types. 200 mL of solution was filtered through each of the capsule filters using a 150 cm length of PharMed® BPT tubing and a peristaltic pump. Filtration was carried out at a speed of 15 rpm. No significant increase in backpressure was observed in the BPT tubing upstream of the filter.

Aliquots were collected throughout the filtration process as follows:

- 0-10 mL
- 10-20 mL
- 20-30 mL
- 30-40 mL
- 40-50 mL
- Hold sample
- Bulk filtrate (~150-200 mL)

The aliquots, hold sample and bulk filtrate were analysed by HPLC for assay and related substances to determine whether there was a loss of assay on the filter membrane or extractables/leachables indicating incompatibility with the membrane or filter housing. The appearance of each aliquot was also recorded.

Results for Adsorptive losses on filtration

Appearance

There was no significant change in appearance between early aliquots, the hold sample or the final post-filtration final bulk using the PES or PDVF filter. From the data obtained, there was no significant difference between PES and PVDF filters when assessing appearance.

Assay (concentration)

The data for the PES membrane filter showed a 103.8% theoretical recovery was achieved for the first aliquot, 0-10 mL, **Table** below. In the second aliquot, 10-20 mL, a slight drop in theoretical assay was observed, 97.9%. However, all other recoveries, including the hold sample and the bulk filtrate, were within 99.3-100.9% of the theoretical concentration. This suggested that there were no significant losses on filtration when using the PES filters.

Table: Assay, PES filter

Sample	Prep 1 (mg/mL)	Prep 2 (mg/mL)	Mean (mg/mL)	Rec./theory* (%)
Early aliquot 1, 0-10 mL	201.305	213.767	207.536	103.8
Early aliquot 2, 10-20 mL	199.818	191.648	195.733	97.9
Early aliquot 3, 20-30 mL	199.990	197.169	198.579	99.3
Early aliquot 4, 30-40 mL	200.784	201.999	201.392	100.7
Early aliquot 5, 40-50 mL	200.734	202.722	201.728	100.9
Hold sample	202.926	200.002	201.464	100.7
Final bulk	200.040	199.650	199.845	99.9

*As percentage of theoretical 200 mg/mL.

The data for the PVDF membrane filter showed a 100.9% theoretical recovery was achieved for the first aliquot, 0-10 mL, **Table** below. All recoveries, including the hold sample and the bulk filtrate, were within 99.1 - 101.9% of the theoretical concentration. This suggested that there were no significant losses on filtration when using the PVDF filters.

Table: Assay, PVDF filter

Sample	Prep 1 (mg/mL)	Prep 2 (mg/mL)	Mean (mg/mL)	Rec./theory* (%)
Early aliquot 1, 0-10 mL	202.952	200.703	201.828	100.9
Early aliquot 2, 10-20 mL	200.986	195.428	198.207	99.1
Early aliquot 3, 20-30 mL	199.488	202.577	201.033	100.5
Early aliquot 4, 30-40 mL	195.978	201.384	198.681	99.3
Early aliquot 5, 40-50 mL	202.805	202.183	202.494	101.2
Hold sample	203.539	204.048	203.793	101.9
Final bull	203.243	201.630	202.436	101.2

*As percentage of theoretical 200 mg/mL.

Conclusion

In conclusion, there was no significant difference in appearance or cysteamine bitartrate theoretical concentration after filtration using PES or PVDF membrane filters.

Comparing the two filter membrane types, PES and PVDF, both behave similarly with no significant loss of active material in the early aliquots. There was slightly more variability in the assay results for aliquots collected after filtration through the PVDF membrane filter (range 99.1 % - 101.9 %) compared to the PES filter data (range 99.3 % - 100.0 %).

Both filter types are appropriate for use when manufacturing the 200 mg/mL cysteamine bitartrate formulation detailed in **Table: Batch details** above. PVDF membrane filters were selected for use in manufacturing the non-GMP technical batch.

BULK SOLUTION STABILITY

The stability of the non-GMP technical batch (lot No: 001/NVB/20) bulk solution was assessed at two storage conditions: refrigerated (2-8°C) and ambient. Volumes of the bulk filtrate sealed in Schott bottles were held at refrigerated (2-8°C) and ambient conditions for up to 48 hours. Bulk solution was assessed by means of appearance, pH and HPLC at T = 0 and three other time-points (T = 15 h, T = 24 h and T = 48 h).

Results

There is no significant change in appearance over the 48 h stability study period when samples were stored at both 2-8°C and ambient conditions.

Assay and related substances

Table: Pre- and Post-filtration assay

Timepoint/storage		Vial 1 cysteamine bitartrate (mg/mL)	Vial 2 cysteamine bitartrate (mg/mL)	Mean cysteamine bitartrate (mg/mL)	Rec./theory (%)[1]	Rec./Pre-filt (%)[2]
001/NVB/20	Pre-filt	205.273	203.270	204.272	102.1	-
001/NVB/20	Post-filt	204.479	203.047	203.763	101.9	99.8

[1]Calculated as percentage of theoretical 200 mg/mL; [2]Calculated as a percentage of recovery v pre-filtration.

Table: Pre- and Post-Filtration related substances

RRT	Pre-filtration	Post-filtration
3.06	0.15	0.14
3.38	<LOQ	<LOQ
Cystamine (base)	1.53	1.57
Total[1]	**1.68**	**1.71**

[1]Sum of related substances ≥0.05%.

Table: Assay, 2-8°C

Timepoint/ storage		Prep 1 (mg/mL)	Prep 2 (mg/mL)	Prep 3 (mg/mL)	Mean (mg/mL)	Theoretical[1] (%)	Rec./ T = 0[2] (%)	Rec./Pre-filt[3] (%)
Initial (T = 0)		203.533	203.726	204.791	204.017	102.0	-	99.9
2-8°C	T = 15 h	206.191	206.621	-	206.406	103.2	101.2	101.0
	T = 24 h	206.784	206.995	-	206.889	103.4	101.4	101.3
	T = 48 h	205.668	206.986	-	206.327	103.2	101.1	101.0

[1]Calculated as percentage of theoretical 200 mg/mL; [2]Calculated as a percentage of recovery v T = 0; [3]Calculated as a percentage of recovery vs pre-filtration.

Table: Assay, Ambient

Time-point/ storage		Prep 1 (mg/mL)	Prep 2 (mg/mL)	Prep 3 (mg/mL)	Mean (mg/mL)	Theoretical[1] (%)	Rec./ T = 0[2] (%)	Rec./Pre-filt[3] (%)
Initial (T = 0)		203.533	203.726	204.791	204.017	102.0	-	99.9
Ambient	T = 15 h	206.512	206.410	-	206.461	103.2	101.2	101.1
	T = 24 h	206.417	206.525	-	206.471	103.2	101.2	101.1
	T = 48 h	205.726	206.602	-	206.164	103.1	101.1	100.9

[1]Calculated as percentage of theoretical 200 mg/mL; [2]Calculated as a percentage of recovery v T = 0; [3]Calculated as a percentage of recovery vs pre-filtration.

Table: Related substances, 2-8°C

RRT	Timepoint			
	Initial (T = 0)	15 h	24 h	48 h
3.06	0.14	0.12	0.14	0.13
3.38	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	1.61	1.52	1.58	1.85
Total[1]	**1.75**	**1.64**	**1.72**	**1.98**

[1]Sum of related substances ≥0.05%.

Table: Related substances, Ambient

RRT	Timepoint			
	Initial (T = 0)	15 h	24 h	48 h
3.06	0.14	0.09	0.09	0.06
3.38	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	1.61	1.63	1.70	2.03
Total[1]	**1.75**	**1.72**	**1.79**	**2.09**

[1]Sum of related substances ≥0.05%.

Conclusions

There was no significant difference in assay or related substances between pre-filtration and post-filtration samples for the technical batch bulk solution stability study.

No significant changes in appearance were observed over the 48 h stability study period for samples stored at 2-8°C or ambient conditions.

There was no significant difference in assay for bulk stability samples over the 48 h time period at both 2-8°C and ambient conditions. All recoveries were within 101.2 - 101.4% (compared to T = 0). A slight increase in total related substances was observed after the 48 h time-point for both 2-8°C and ambient conditions. This was due to an increase in cystamine (base) impurity.

2.1.P.2.6 Process validation and/or evaluation

Pre-filtration bioburden testing of cysteamine bitartrate 200 mg/mL was validated based upon the European Pharmacopoeia (2.6.12) methodology. To show suitable validation of the method, growth of the five designated compendial Challenge microorganisms (and 1 house organism) were assessed and evaluated. The challenge microorganisms and incubation period were:

Challenge Microorganism	Temperature	Duration
Staphylococcus aureus, ATCC 6538	30-35°C	64 hours 59 minutes
Pseudomonas aeruginosa, ATCC 9027		
Bacillus subtilis, ATCC 6633		
Micrococcus luteus (house organism)		
Candida albicans, ATCC 10231	20-25°C	67 hours 15 minutes
Aspergillus brasiliensis, ATCC 16404		

Results

CHALLENGE MICROORGANISM	CFU	CFU +VE CONTROL	PERCENTAGE OF CONTROL	PASS/ FAIL
Staphylococcus aureus	60	52	115.38	PASS
Pseudomonas aeruginosa	46	53	86.79	PASS
Bacillus subtilis	45	58	77.59	PASS
Candida albicans	38	46	82.61	PASS
Aspergillus brasiliensis	21	21	100	PASS
Micrococcus luteus	71	80	88.75	PASS
Negative control	0			PASS

The positive control plates were within <100 CFU specification, which confirms a valid recovery concentration of organisms inoculated onto the membrane.

The percentage recoveries of all organisms on the membrane following exposure to cysteamine and neutralisation buffer are all within the 50-200% criteria.

Conclusion: The data generated supports the method suitability for the challenge microorganisms and demonstrates successful neutralisation of any antimicrobial activity present in the cysteamine samples. This method is therefore suitable for in-process testing in support of manufacture.

Thawing process

USP 790 test was performed to check that the IMP solution was clear of contamination. 20 vials were thawed at ambient temperature for an hour and were then manually agitated each vial for 30 seconds and checked for any particulates in solution. If particulates were evident, the vial was agitated again for a further 30 seconds to ensure the solution was clear and there was no material. Any particulates observed after second agitation was considered as a foreign to the solution and was marked as failed test. During various analytics testing and stability testing, thaw time for IMP vials noted to be 25 minutes at ambient and 40 minutes at 2-8°C.

2.1.P.3 Control of excipients

2.1.P.3.1 Specifications

Water for irrigation (water for injection in bulk) and sodium hydroxide were the excipients that were used in the manufacture of cysteamine bitartrate 200 mg/mL. Both excipients are complaint European Pharmacopoeia (Ph.Eur.) and the specifications are provided below.

Specification for water for irrigation

Product details			
Item Master Number:	GRMA0042	**Status:**	Active
Description:	Water for irrigation (water for injection in bulk)		
Standard Expiry Period:	730	**Storage:**	Ambient (15-25°C)
Supplier:	TPS	**Supplier Part Number:**	UKF7114
Grade:	Ph Eur	**Drawing reference:**	N/A

Sample requirements			
Release:	1 bottle	**Full Compendial:**	N/A
Retest:	N/A	**Retain:**	None

Approval requirement			
Test 1:	Appearance: Clear, colourless liquid	**Test 2:**	Complies with Pharmacopeial requirements for TOC
Test 3:	Complies with Pharmacopeial requirements for Conductivity	**Test 4:**	0
Endotoxin Level:	From CofA	**Calculation of Bioburden:**	From CofA

Documentation requirements			
TSE/BSE Statement:	Yes	**Certificate of Analysis/Conformity:**	Yes
Certificate of Irradiation:	No	**Certificate of Sterility:**	No
Other 1:	NIA	**Other 2:**	NIA

Specification for sodium hydroxide

Product details			
Item Master Number:	GRMA0105	**Status:**	Active
Description:	Sodium hydroxide: Ph. Eur, BP, FCC, JP, NF, E524 (CAS # 1310-73-2)		
Standard Expiry Period:	730	**Storage:**	Ambient (15-25°C)
Supplier:	VWR International Ltd	**Supplier Part Number:**	1.06482.1000
Grade:	BP, Ph Eur, NF	**Drawing reference:**	N/A

Sample requirements			
Release:	1g	**Full Compendial:**	30 g
Retest:	N/A	**Retain:**	60 g

Approval requirement			
Test 1:	Appearance: White to off-white powder	**Test 2:**	Complies with Ph Eur Identity Tests
Test 3:	N/A	**Test 4:**	N/A
Endotoxin Level:	Not Applicable	**Calculation of Bioburden:**	Not Applicable

Documentation requirements			
TSE/BSE Statement:	Yes	**Certificate of Analysis/Conformity:**	Yes
Certificate of Irradiation:	No	**Certificate of Sterility:**	No
Other 1:	NIA	**Other 2:**	NIA

2.1.P.3.2 Analytical procedures

Not applicable

2.1.P.3.3 Validation of the analytical procedures

Not applicable

2.1.P.3.4 Justification of specifications

Not applicable

2.1.P.3.5 Excipients of animal or human origin

No excipients are of human or animal origin. Refer to **Section 3.1.A.2**.

2.1.P.3.6 Novel excipients

None involved.

2.1.P.4 Control of the investigational medicinal product

2.1.P.4.1 Specifications

Product shelf-life specifications for cysteamine bitartrate 200 mg/mL vials

Test	Method	Specification
Appearance	Visual, C/TE/8257	Clear solution: Colourless, free from visible particles
pH	C/EQ/8007 Ph Eur 2.2.3, USP<791>	Report results
Osmolality	C/EQ/8009 Ph. Eur. 2.2.35, USP <785>	Report results
Identification (Retention Time)	QCP003 (HPLC)	Retention peak compares to the reference standard
Identification (DAD Spectra)	QCP003 (HPLC)	λ max in the reference solution and in the sample solution are the same within ±3 nm
Assay	QCP003 (HPLC)	90.0 – 105.0%
Purity	QCP003 (HPLC)	NLT 95%
Impurities	QCP003 (HPLC)	Cystamine (base): ≤5.0% Any single unknown impurity: ≤0.15% Total unknown impurities: ≤0.5% Total impurities: ≤5.0%
Volume in Container (Extractable Volume)	AMRI C/GE/8516 Ph Eur 2.9.17, USP<697>	NLT 2.2 mL
Particulate Matter	C/EQ/8042 Ph Eur 2.9.19 Method 1 USP<788> Method 1	Complies with Ph. Eur./USP
Sterility	Charles River Laboratories Ireland Ph Eur 2.6.1, USP<71>	Sterile
Endotoxins	M/TE/5273 Ph Eur 2.6.14, USP<85>	NMT 10 EU/mL

Release specifications for cysteamine bitartrate 200 mg/mL vials

Test	Method	Specification
Appearance	Visual, C/TE/8257	Clear solution: Colourless, free from visible particles
pH	C/EQ/8007 Ph Eur 2.2.3, USP<791>	Report results
Osmolality	C/EQ/8009 Ph. Eur. 2.2.35, USP <785>	Report results
Identification (Retention Time)	QCP003 (HPLC)	Retention peak compares to the reference standard
Identification (DAD Spectra)	QCP003 (HPLC)	λ max in the reference solution and in the sample solution are the same within ±3 nm
Assay	QCP003 (HPLC)	95.0 – 105.0%
Purity	QCP003 (HPLC)	NLT 95%
Impurities	QCP003 (HPLC)	Cystamine (base): ≤5.0% Any single unknown impurity: ≤0.15% Total unknown impurities: ≤0.5% Total impurities: ≤5.0%
Volume in Container (Extractable Volume)	AMRI C/GE/8516 Ph Eur 2.9.17, USP<697>	NLT 2.2 mL
Particulate Matter	C/EQ/8042 Ph Eur 2.9.19 Method 1 USP<788> Method 1	Complies with Ph. Eur./USP
Sterility	Charles River Laboratories Ireland Ph Eur 2.6.1, USP<71>	Sterile
Endotoxins	M/TE/5273 Ph Eur 2.6.14, USP<85>	NMT 10 EU/mL

2.1.P.4.2 Analytical procedures

The following analytical methods were carried out by Albany Molecular Research Inc. (Glasgow) Limited [AMRI] for cysteamine bitartrate, 200 mg/mL sterile drug product sealed in a 2 mL vial (fill volume 2.5 mL). All the analytical method verification procedures were based on AMRI standard operating procedures (SOPs) for each method and are designed to comply with USP and Ph. Eur. Requirements intended to support the technical studies, GMP batch release and clinical stability studies of cysteamine bitartrate, 200 mg/mL drug product.

Sample preparation

As samples were stored frozen, the following sample preparation was performed for all the analytical procedures:

- Thaw sample vials at ambient conditions for 1 hour.
- Manually agitate each vial for 30 seconds and check for any particulates in solution.
- If particulates are evident agitate again for a further 30 seconds to ensure material is fully in solution and no visible particulates are observed.

APPEARANCE

Clear, colourless solution, free from visible particulate matter.

Method: Visual observation.

Procedure

- Sample solutions were assessed as it was. No further dilution or manipulation of the sample was performed.
- For each test sample vial, the container was held by its top, and carefully swirled the contents so that the solution into contact with all surfaces including the stopper.
- Looked at the container contents in an area with suitable lighting for approximately 5 seconds each. Recorded the results for each test sample vial in terms of colour, clarity and level of particulates present.
- Compared colour and clarity against a sample of a similar volume of Water for Irrigation. This comparator was used to assess any colour or turbidity in the product samples.

Method verification by: Precision (Method Repeatability and Intermediate Precision)

Acceptance criteria:

- All sample vials contain ‘clear, colourless solution, free from visible particulate matter’.
- Results achieved between analysts are consistent.

pH DETERMINATION

Method: pH determination by combination electrode.

Procedure

- Ensure the calibration of the pH meter is suitable, by assessing the certified pH standard solutions (4.01, 7.00 & 10.00).
- Place the electrode into the sample vial and allow to equilibrate. Record the measured pH.

Method verification by: Precision (Method Repeatability and Intermediate Precision)

Acceptance criteria:

- A pH target ~5.5 is expected for the test samples therefore the pH standards were chosen to fully encompass this range.

The Precision for pH will comply if:

- Repeatability results, RSD ≤1% (n = 6, both analysts)
- Intermediate precision, RSD ≤2% (n =12)

OSMOLALITY

Method: Osmolality determination by depression in freezing point method (Gonotec Osmomat 3000 model).

Procedure

- Prior to testing, perform a 1:10 v/v dilution (1 part drug product, 9 parts WFI). Diluted samples should be tested and reported as is, without applying any dilution factor.
- Ensure the calibration of the Osmometer meter is suitable, by assessing water (blank) and certified Osmolality standard solutions.
- Transfer the defined amount of sample in the sample tube and read the osmolality.

Method verification by: Precision (Method Repeatability and Intermediate Precision)

Acceptance criteria

The Precision for Osmolality will comply if:

- Repeatability results show an RSD of <3% (n = 18).
- intermediate precision shows an RSD of <3% (n = 36).

SUB-VISIBLE PARTICULATES MEASUREMENT

Method: by light obscuration.

Procedure

- Prepare 3 test solutions, each by pooling 10 sample vials into a single clean container. Pooled samples should give a volume of ~25 mL each. Perform a 1:5 v/v dilution on each pooled sample (i.e. 1 part pooled drug product and 4 parts Water for Irrigation). The diluted samples will be assessed.
- Ensure the calibration of the HIAC 9703+ Liquid Particle Counter is suitable and is within it calibration/maintenance period.
- Analyse each of the three diluted test samples prepared in 4.1.1. The instrument software will automatically adjust results for the dilution performed.

Method verification by: Precision (Method Repeatability)

Acceptance criteria

The assessment will comply if:

- Each sample set of samples (triplicate) meet the pharmacopoeial requirements of <6000 particles/vial at ≥10 µm and <600 particles/vial at ≥25 µm are achieved.

Conclusion

The method for appearance, pH, osmolality, and sub-visible particles measurement of cysteamine bitartrate were successfully verified and demonstrated to be suitable for the assessment of cysteamine bitartrate, 200 mg/mL drug product.

2.1.P.4.3 Validation of the analytical procedures

Validation of the HPLC method for determination of assay and related substances

An HPLC method was obtained by **Novabiotics Ltd.** from our cysteamine IMPD v 1.0 for the oral dosage form. The method was transferred to AMRI (Glasgow) and used in support of the formulation development activities. Validation exercise was carried out to confirm the method is suitable for the determination of assay and related substances of cysteamine bitartrate in 200 mg/mL cysteamine bitartrate drug product, **Table** below. The method was validated in accordance with ICH guideline Q2 (R1) as suitable for the phase (I) of clinical development.

Table

Component	Concentration (mg/mL)
Cysteamine bitartrate	200
WFI	q.s.
10 M sodium hydroxide	q.s.

Validation requirements

To following parameters were evaluated:

1. System suitability
2. Specificity (including forced degradation assessment with light and heat)
3. Linearity
4. Accuracy
5. Precision
6. Identity
7. Sensitivity (limit of detection and limit of quantification)
8. Robustness: Solution stability (up to 3 days) and intermediate precision

Materials, reagents, and equipment

All materials/reagents were HPLC grade as appropriate, and equipment were suitable for use.

Materials and reagents

Details	Supplier	Batch/lot number
Cysteamine bitartrate API	Cambrex	Lot: 751111
200 mg/mL cysteamine bitartrate Drug Product	AMRI	Batch Number: 001/NVB/20
Methanol	Fisher	2066189
Purified Water	Millipore	Q084
HPLC Grade Acetonitrile	VWR	20J061957
Sodium Dodecyl Sulphate	Sigma Aldrich	
85% Phosphoric Acid	Sigma Aldrich	

Equipment

HPLC system- Agilent HP 1100/1200 or equivalent with VWD and DAD
Thermo Scientific, BDS Hypersil C18, 250 x 4.6 mm, 5 µm
Analytical balances
Call A volumetric glass pipettes
Positive displacement pipettes, Gilson or equivalent
Volumetric glassware, various

HPLC METHOD

HPLC conditions

Column: Thermo Scientific, BDS Hypersil C18, 250 x 4.6 mm, 5 µm
Column temperature: 25°C
Detection wavelength: 210 nm
Autosampler temperature: 5°C
Flow rate: 1.4 mL/min
Injection volume: 100 µL
Mobile phase A: 40 mM sodium dodecylsulphate in 38:32:30:0.14, water: methanol:acetonitrile:phosphoric acid, v:v:v:v
Mobile phase B: 100% acetonitrile
Diluent: 100% water
Working concentration: Cysteamine bitartrate, 1.5 mg/mL
Needle wash: Acetonitrile/water (80:20)

The gradient program for the analysis is shown in **Table** below.

Time (min)	**Mobile phase (A) %**	**Mobile phase (B) %**
0	100	0
7	100	0
27	40	60
32	40	60
35	100	0
45	100	0

Solution preparation for HPLC

Alternate volumes may be prepared as required.

Mobile phase A (1 L)
Accurately weigh approximately 11.52 g of sodium dodecyl sulphate and add to 380 mL of water to dissolve. To this add 320 mL Methanol, 300 mL Acetonitrile and 1.4 mL 85% Phosphoric Acid then mix thoroughly.

Mobile phase B
100% Acetontrile.

Diluent: 100% water.

Needle wash: Add 800 mL of acetonitrile and 200 mL of water into a 1 L duran and mix thoroughly.

Standard solutions (cysteamine bitartrate)

Prepare in duplicate. Accurately weigh approximately 15 mg cysteamine bitartrate reference standard into a 10 mL volumetric flask. Dilute to volume with diluent and mix thoroughly. These are the working standard solutions with a nominal cysteamine bitartrate concentration of 1.5 mg/mL.

Drug product solution (200 mg/mL cysteamine bitartrate drug product, Batch: 001/NVB/20)

Using a positive displacement pipette, transfer 150 µL of drug product to a 20 mL volumetric flask and make to volume with diluent.

Method Validation

SYSTEM SUITABILITY

A system suitability exercise was performed, before any validation exercise commences. This procedure was to demonstrate that system performance meets the standards required by the method.

Solution preparation

Standard solutions were prepared as described above (standard solutions).

Analysis and acceptance criteria

Blank (diluent) injections were performed until a stable baseline, free from interfering peaks is obtained. This was followed by six replicate injections of cysteamine bitartrate standard solution 1 and duplicate injections of standard solution 2. The following parameters were

monitored throughout the validation. The data obtained during validation may be used to refine the acceptance criteria for routine use of the method.

Table: System suitability

Solution	System suitability parameter	Nominal acceptance criteria
Blank solution	Specificity	Absence of interfering peaks
Cysteamine bitartrate Standard 1 solution (6 consecutive injections)	Retention time precision	%RSD ≤2.0%
	Peak area precision	%RSD ≤2.0%
	Peak asymmetry (USP)	≤2.0
	Theoretical plate count (USP)	Read and Record
Standard 2 solution (duplicate injections)	Standard agreement = $\frac{\text{Area St 2}}{\text{Area St 1}} \times \frac{\text{Weight Std 1}}{\text{Weight Std 2}} \times 100$	98.0 -102.0%
Standard 2 solution	Retention time precision throughout the analysis	%RSD ≤2.0%
	Peak area precision throughout the analysis	%RSD ≤2.0%

Results

The system suitability results obtained throughout the validation exercise are shown in **Table** below. The blank (diluent) chromatograms were stable with no significant interference before starting sample sequences. The RSD for the retention time and peak area for five replicate injections of Standard 1 was ≤2.0% and standard agreement was 100 ± 2.0% as required. The RSD of all Standard 2 injections (bracketing) within any run was also ≤2.0% indicating good system performance throughout the runs.

System suitability

Analysis	Standard 1				Standard agreement	Standard 2	
	RT precision	Peak area precision	Asymmetry (EP)	Plates (EP)		Precision	
						RT	Peak area
1	0.1	0.3	1.63	11485	99.6	0.0	0.3
2	0.1	0.3	1.75	10615	100.1	0.0	0.3
3	0.0	0.1	1.56	12627	99.4	0.0	0.4
4	0.0	0.1	1.68	11121	99.8	0.1	0.1
5	0.1	0.1	1.70	10809	100.0	0.1	0.2
6	0.0	0.1	1.79	9659	100.3	0.2	0.0
7	0.0	0.1	1.74	10669	99.9	0.1	0.2
8	0.1	0.0	1.84	10099	100.1	0.1	0.6
9	0.1	0.1	1.68	11284	100.1	0.0	0.8
10	0.1	0.1	1.63	11490	100.2	0.0	0.7
Acceptance:	≤2.0%	≤2.0%	Record	Record	100 ± 2.0%	≤2.0%	≤2.0%

SPECIFITY

Specificity was demonstrated by acceptable accuracy in the presence of formulation excipients.

Specificity was also demonstrated by evaluating the chromatography to ensure there is no interference of the main analyte peak from any excipients in the formulation, possible impurities/degradation products or sample solvent.

Solution preparation

Degradant specificity

Vials of drug product were subjected to heat and light stress according to Table below (stress conditions) and analysed to ensure that no peaks have formed which may interfere with the main analyte peak. If after storage for the required time, no additional peaks are observed, no further attempts will be made to degrade the drug product.

Stress conditions

Storage condition	Description	Time-point (weeks or exposure to light)
50°C	Drug product	After 24 hours, 1 week and up to 2 weeks
Photostability	Drug product	>200 Wh/m2 and >1.2 million lux hours
	Drug product control (protected from light)	>200 Wh/m2 and >1.2 million lux hours

Following storage, the solutions were prepared for analysis as described for drug product.

Analysis and acceptance criteria

Diluent, stressed and non-stressed drug product solution were analysed using PDA with data collection 190 - 400 nm.

- The main peak should have no interference from other extraneous components.
- There should be demonstrated resolution of components from each other by chromatographic separation.
- Cysteamine bitartrate peak purity will be assessed. Using the chromatographic software, a peak purity match of >950 will demonstrate peak purity for cysteamine bitartrate.

With respect to sample diluent

There were no peaks in the diluent which would interfere with the quantification of cysteamine bitartrate or related substances in sample solutions.

With respect to excipients or potential degradants

There were no peaks in the non-stressed or stressed placebo solutions which would interfere with the identification/integration of cysteamine bitartrate or related substances, See **Figure** below.

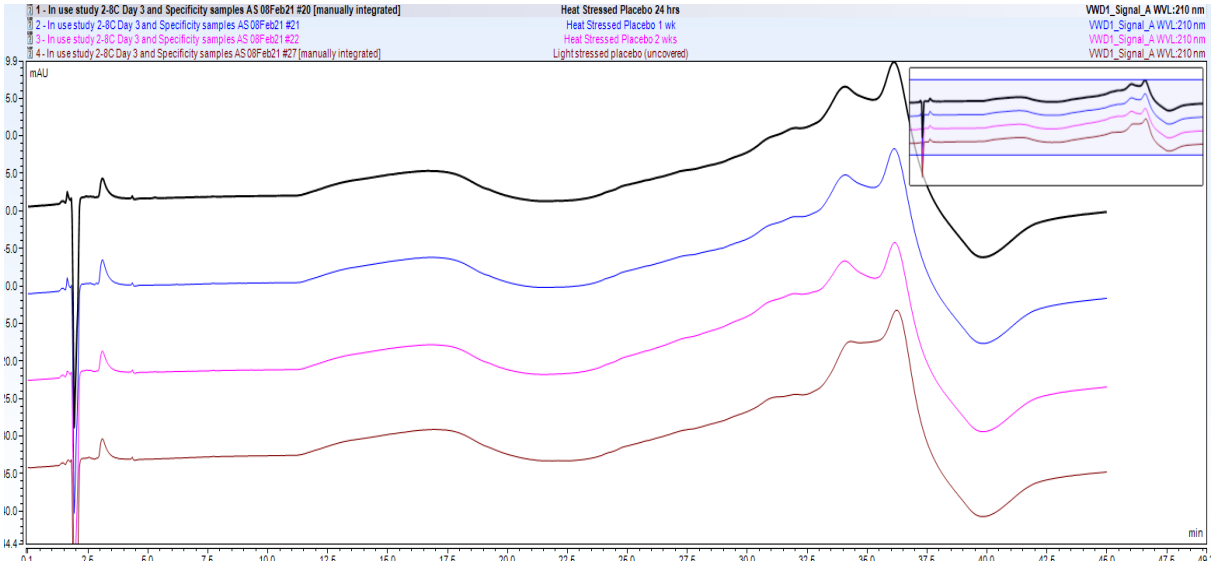


Figure: Placebo solution chromatograms

Table: Assay data for stressed/non-stressed drug product

Details	Content (mg/mL)	Recovery/Theoretical* (%)
Heat stressed (1 day)	201.400	100.7
Heat stressed (1 week)	199.208	99.6
Heat stressed (2 weeks)	200.454	100.2
Light stressed (Uncovered)	200.323	100.2
Light stressed (Covered)	202.243	101.1

**Calculated versus a theoretical concentration of 200 mg/mL.*

There is no significant change in the assay recoveries over the 2-week period for the heat stressed samples.

There is no significant change in the assay recoveries for the light stressed uncovered sample vs the light stressed covered sample.

Table: Purity profiles for stressed/non-stressed drug product

RRT	Area %					
	Control[1]	**Light stressed (Uncovered)**	**Light stressed (Covered)**	**Heat stressed (1 day)**	**Heat stressed (1 week)**	**Heat stressed (2 weeks)**
RRT 0.72	0.04	0.04	0.04	0.04	0.04	0.08
RRT 0.73	0.05	0.04	0.04	0.04	0.04	0.04
RRT 0.84	ND	0.06	0.06	0.06	0.08	0.08
RRT 1.18	0.02	0.02	0.02	0.02	0.02	0.02
RRT 1.32	0.03	0.02	0.02	0.02	ND	ND
RRT 1.57	0.03	0.03	0.03	0.03	0.04	0.05
RRT 3.49	0.12	ND	ND	0.01	ND	ND
RRT 3.71	0.03	0.01	ND	ND	0.02	0.02
Cystamine (base)	1.85	2.14	2.04	2.33	2.50	2.38
Total[2]	**2.02**	**2.20**	**2.10**	**2.43**	**2.58**	**2.58**

[1]Control sample results are taken from precision sample 1 data, analysis performed on a different day/system; [2]Sum of all related substances ≥0.05%, totals taken from chromatographic software.

When comparing the heat stressed sample at 1 day to the heat stressed sample at 1 week, there is an increase of >0.1% rel area for the cystamine (base) however, the % rel area of the cystamine (base) at 2 weeks is comparable with the 1 day. As seen in the precision and intermediate precision stages, there is variability between vials for the cystamine (base) due to the inconsistent rate that the vials reach freezing point in storage.

There is a significant increase in cystamine (base) for all samples when compared to the control sample however, this is also due to the variability been vials for the cystamine (base).

Table: Cysteamine bitartrate peak match

Solution	Peak match purity	Compared to average bracketing standards (%)
Heat stressed sample (1 week)	945	100.1
Heat stressed sample (2 weeks)	942	99.8
Light stressed sample (Uncovered)	942	99.8
Light stressed sample (Covered)	942	99.8

Peak match is not >950 indicating there is a possibility of co-elution of a related substance. However, for the forced degradation samples, the peak match is not reduced indicating that if there is any co-elution it is not from a degradation product and therefore the method can still be considered stability indicating.

No peak match data obtained for 24 h timepoint due to sample being discarded in error prior to repeat of analysis [**Refer to Section 'Investigation': Specificity at the end of this section (Page = 148)**].

IDENTITY

The suitability of the method to determine identity was assessed.

Solution preparation

None required, data from **specificity** was used.

Analysis and acceptance criteria

Identity for cysteamine bitartrate by HPLC requires corresponding retention time between the sample and reference material and corresponding UV spectra between the sample and reference material.

Based on the data from **specificity** an appropriate criterion for retention time difference between sample and reference standard was produced.

The UV spectra from the reference standard and a sample was reported, identifying any λmax from the spectra and suggested specification.

LINEARITY

1. Assay level

The linearity of the response to cysteamine bitartrate concentration was determined over the range 60 – 140% of the 1.5 mg/mL working concentration.

Solution preparation

A stock solution was prepared at 200% of the working concentration by accurately weighing approximately 150 mg cysteamine bitartrate reference standard into a 50 mL volumetric flask. This was dissolved in and diluted to volume with diluent. The linearity series were prepared by dilution of the stock solution, with diluent, according to the **Table** below.

Preparation of linearity solutions, assay level

Linearity solution	Solution (%)	Volume stock solution (mL)	Final volume (mL)	Theoretical [cysteamine bitartrate] (mg/mL)
1	60	3	10	0.90
2	80	4	10	1.20
3	100	5	10	1.50
4	120	6	10	1.80
5	140	7	10	2.10

Analysis and acceptance criteria

Single injections of each solution were performed in order of ascending concentration. A blank (diluent) injection was performed to assess any carry-over, followed by a single injection of each linearity solution in order of descending concentration.

A plot of peak area versus concentration was obtained and linear regression analysis by the method of least squares performed. The correlation coefficient, equation of the line and intercept were reported. A regression coefficient (R) of ≥ 0.999 should be obtained.

The % recovery of each individual linearity concentration level (n=10), were calculated against bracketing standards. The % recovery for each injection should be within 98.0 – 102.0%.

Results: Assay level

The response was linear in the range of 0.9 -2.1 mg/mL cysteamine bitartrate or 60 -140% of the working concentration, **Table and Figure** below.

Table: Linearity of response to BST-236 concentration

Target (%)	[Cysteamine bitartrate] (mg/mL)	Perak area (mAU/min)	Response factor*	% recovery
60	0.9109	45.569	50.0	100.4
60	0.9109	45.114	50.6	101.6
80	1.2145	61.450	50.6	101.5
80	1.2145	61.366	50.5	101.1
100	1.5182	76.198	50.2	100.7
100	1.5182	75.734	49.9	100.1
120	1.8218	91.140	50.0	100.3
120	1.8218	91.548	50.3	100.8
140	2.1254	105.964	49.9	100.0
140	2.1254	150.947	49.8	100.0
		Mean	50.18	
		RSD (%)	0.6	

**Peak area divided by concentration.*

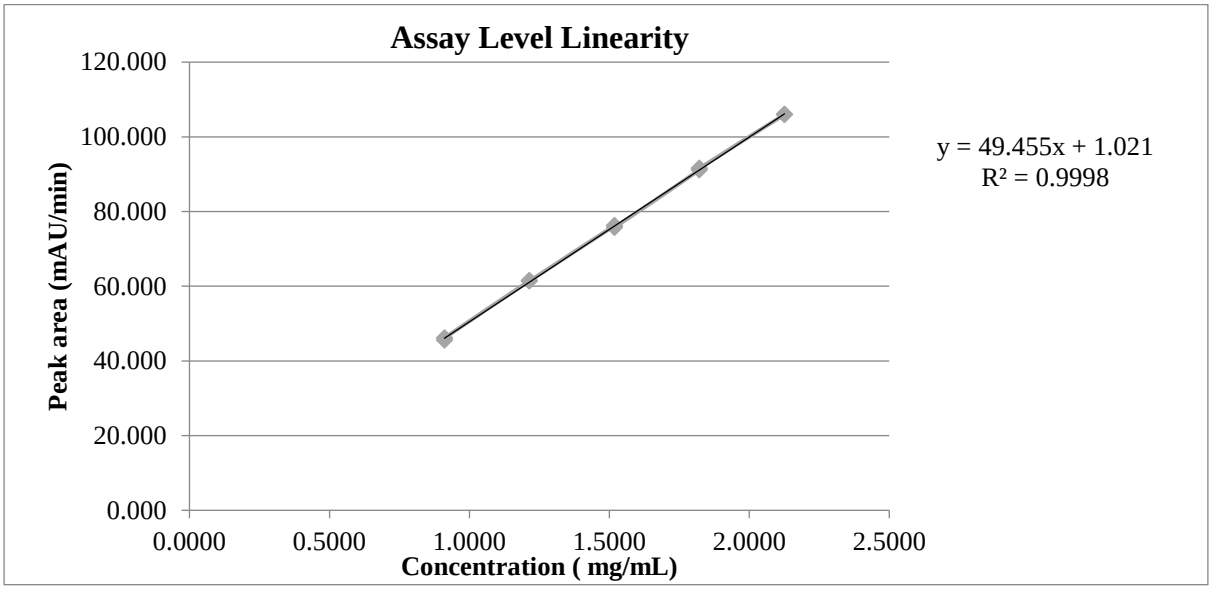


Figure: *Linearity of response to cysteamine bitartrate concentration*

The correlation coefficient, R was 1.000 and met the acceptance criterion R≥0.999. The intercept was 1.4% of the nominal 100% working concentration, which meets the desired ≤2.0% criteria. The RSD for the response factors was also acceptable (≤2.0%), indicating no bias over the chosen concentration range. All recoveries at each concentration level pass the criteria of 98.0 -102.0%.

2. Related substance level (unknown impurities)

The linearity of response at related substance level were assessed over the range 0.02 – 1.0% of the working concentration.

Solution preparation

A 2% cysteamine bitartrate solution was prepared by transferring 2 mL of standard solution to a 100 mL volumetric flask and diluting to volume with diluent. The linearity series was prepared by dilution of the 2 % solution with diluent according to the **Table** below.

Table: Preparation of linearity series, related substance level

%Nominal working concentration	Volume 2% stock (mL)	Final volume (mL)	[Cysteamine bitartrate] Theory (µg/mL)
1.00	5	10	15.0
0.50	5	20	7.5
0.20	1	10	3.0
0.10	1	20	1.5
0.05	0.5	20	0.75
0.02	1	100	0.3

Analysis and acceptance criteria

Duplicate injections of each linearity solution were performed, bracketed by standard injections. A plot of peak area versus concentration was obtained and linear regression analysis by the method of least squares performed. The correlation coefficient, equation of the line and intercept were reported. A regression coefficient (R) of ≥0.99 should be obtained.

Note: The data obtained for the related substance level linearity solutions was also used to assess method sensitivity, See below: Sensitivity.

Results: Related substance level

The response was linear over the range 0.02-1.0% of the working concentration. Table and Figure below, with a correlation coefficient, R of 1.00, meeting the acceptance criterion R≥0.99.

Table: Linearity of response to cysteamine bitartrate concentration, 0.02 - 1.00%

Target (%)	[Cysteamine bitartrate] (µg/mL)	Perak area (mAU/min)	% Recovery	S/N
0.02	0.303	0.013	84.4	9
0.02	0.303	0.013	82.3	9
0.05	0.758	0.036	89.7	22
0.05	0.758	0.034	84.2	21
0.10	1.516	0.068	85.4	43
0.10	1.516	0.068	85.3	42
0.20	3.033	0.150	94.1	91
0.20	3.033	0.148	92.6	91
0.50	7.582	0.382	95.8	232
0.50	7.582	0.379	95.0	230
1.00	15.164	0.766	96.0	465
1.00	15.164	0.768	96.3	466

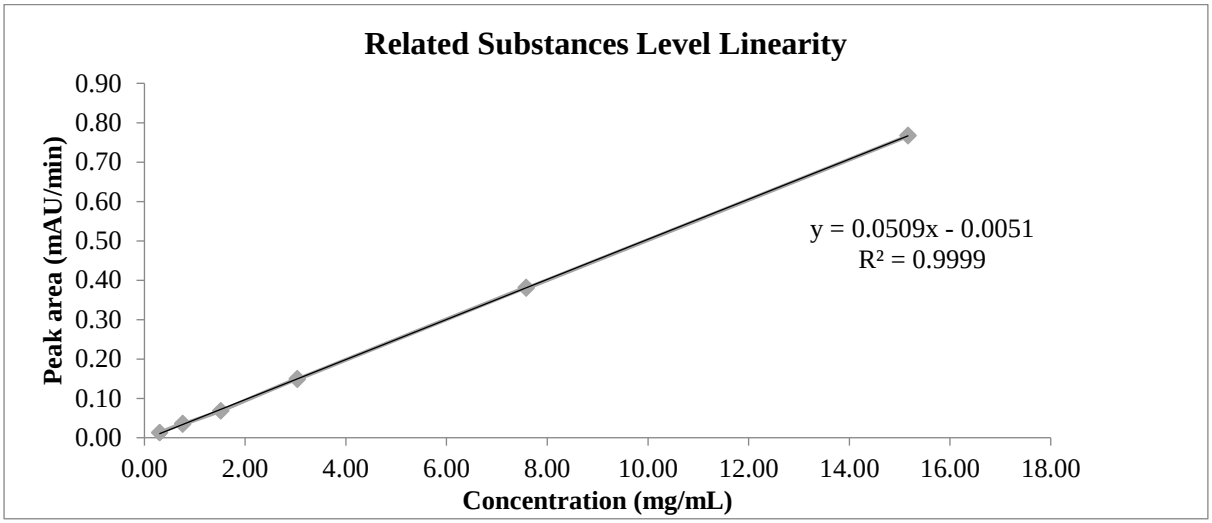


Figure: Linearity of response to cysteamine bitartrate concentration, 0.05 - 1.00%.

ACCURACY

Nine solutions of cysteamine bitartrate at 70%, 100% and 130% of the nominal working concentration (1.5 mg/mL) were prepared and made to volume with diluent and assessed against verified standards.

Solution preparation

At each level three solutions were prepared as detailed in the Table below.

Preparation of accuracy solutions

%Nominal working concentration	Weight cysteamine bitartrate (mg)	Final volume (mL)	[Cysteamine bitartrate] Theory (µg/mL)
70	10.5	10	1.05
100	15.0	10	1.50
130	19.5	10	1.95

Analysis and acceptance criteria

A single injection of each solution was performed and the %recovery of cysteamine bitartrate calculated against a verified standard solution.

The recovery was calculated as follows:

$$\%\text{recovery} = \frac{As}{Ar} \times \frac{Wr}{DFr} \times \frac{DFs}{Ws} \times 100$$

Where:

As = Cysteamine bitartrate peak area in sample solution
Ar = Cysteamine bitartrate mean peak area in standard solution (bracketed)

Wr = Weight cysteamine bitartrate in standard (mg)
Ws = Weight cysteamine bitartrate in sample (mg)
DFr = Dilution factor of standard solution (mL) (10 in preparation described)
DFs = Dilution factor of sample solution (mL) (10 in preparation described)
100 = Conversion to per cent

Note: No potency correction will be applied as comparing like with like.

- All recoveries should lie within 98.0 – 102.0% of the theoretical.
- Accuracy will be expressed as the mean (n = 9) recovery to one decimal place.
- The %RSD of the mean (n = 3) recovery at each concentration level must be ≤2.0%.

Results

The recovery for each solution was 99.7 - 100.7% and the RSD at each concentration level was ≤2.0% as required**, Table** below. The overall accuracy of the method (n = 9) was 100.4%.

Table: Accuracy

Details		Recovery* (%)
70%	Solution 1	100.5
	Solution 2	100.6
	Solution 3	100.7
	Mean	100.6
	RSD	0.1
100%	Solution 1	100.2
	Solution 2	100.5
	Solution 3	100.5
	Mean	100.4
	RSD	0.2
130%	Solution 1	100.4
	Solution 2	100.0
	Solution 3	99.7
	Mean	100.1
	RSD	0.4

**Calculated against a qualified reference standard.*

PRECISION

Repeatability of the analytical method was assessed by analysing six preparations of drug product.

Solution preparation

The sample solutions were prepared as per standard solutions for drug product (see above) and analysed against a verified standard solution. Standard and sample preparations from this experiment may be used for sample solution stability.

Analysis and acceptance criteria

The assay results (mg/mL) for the drug product will be calculated as follows:

$$[\text{Cysteamine Bitartrate}]\ (\text{mg/mL}) = \frac{As}{Ar} \times \frac{Wr}{DFr} \times DF \times P$$

Where:

As = Cysteamine bitartrate peak area in sample solution
Ar = Cysteamine bitartrate mean peak area in standard solution (bracketed)
Wr = Weight cysteamine bitartrate in standard (mg)
DFr = Dilution factor of standard solution (mL) (10 for preparation described)
DFs = Dilution factor of sample solution (mL) (133.3333 for preparation described)
P = Purity value of reference standard, in decimal form

The mean and %RSD were calculated, and the results assessed against the following acceptance criteria:

- The %RSD for drug product content should be ≤2.0%.
- The %RSD for individual related substances ≥0.05 but <0.2% should be ≤20%.
- The %RSD for individual related substances ≥0.2% should be ≤10%.
- The %RSD for the total related substances should be ≤5%.

Results

The %RSD for the cysteamine bitartrate content of the six preparations was ≤2.0% as required, see **Table** below.

Table: Precision, cysteamine bitartrate assay

Details	Cysteamine bitartrate (mg/mL)
Preparation 1	201.872
Preparation 2	201.964
Preparation 3	201.261
Preparation 4	202.106
Preparation 5	201.584
Preparation 6	201.402
Mean	**201.698**
RSD	**0.2**

All detected related substances are shown in **Table** below. For related substances ≥0.2%, RSD was ≤10%. For related substances ≥0.05 and ≤2.0%, RSD was ≤10%. The RSD for total related substances failed specification of ≤5%. due to the variable cystamine (base) seen throughout the technical batch [**Refer to Section 'Investigation': Variation in cystamine (base) between vials at the end of this section (Page = 153)**].

Table: Precision, Related substances area %

RRT	Rel Area %						Mean	%RSD
	1	2	3	4	5	6		
RRT 0.72	0.04	0.05	0.05	0.05	0.04	0.04	0.05	6
RRT 0.73	0.05	0.05	0.05	0.05	0.05	0.05	0.05	4
RRT 1.18	0.02	0.02	0.03	0.02	0.02	0.02	<LOQ	17
RRT 1.32	0.03	0.04	0.03	0.03	0.03	0.03	<LOQ	10
RRT 1.57	0.03	0.03	0.03	0.03	0.03	0.03	<LOQ	9
RRT 3.49	0.12	0.12	0.12	0.12	0.12	0.12	0.12	2
RRT 3.71	0.03	0.03	0.03	0.03	0.03	0.03	<LOQ	9
Cystamine (base)	1.85	1.87	1.68	1.84	1.66	1.98	1.81	7
Total*	**2.02**	**2.09**	**1.90**	**2.06**	**1.83**	**2.15**	**2.03**	**6**

**Sum of related substance ≥0.05%, totals taken from chromatographic software.*

SENSITIVITY

LOQ/LOD determination

The limit of quantitation and limit of detection were determined using the data obtained during the related substance linearity assessment.

Solution preparation: Not required.

Analysis and acceptance criteria

The mean peak height for each solution was compared to the mean baseline noise for the placebo solution analysis. A plot of signal-to-noise versus concentration was obtained and linear regression analysis by the method of least squares performed. The equation of the line was used to determine the limit of detection, S/N = 3 and limit of quantitation, S/N = 10.

The %recovery of cysteamine bitartrate was calculated for each solution in the series as follows:

$$\%\text{recovery} = \frac{\text{As}}{\text{Ar}} \times \frac{\text{Wr}}{\text{DFr}} \times \frac{\text{DFs}}{\text{Ws}} \times 100$$

Where:

As = Cysteamine bitartrate peak area in sample solution
Ar = Cysteamine bitartrate mean peak area in standard solution (bracketed)
Wr = Weight cysteamine bitartrate in standard (mg)
Ws = Weight cysteamine bitartrate in sample (mg)
DFr = Dilution factor of standard solution (mL) (10 in preparation described)
DFs = Dilution factor of sample solution (mL) (various)
100 = Conversion to per cent

Note: No potency correction will be applied as comparing like with like.

The recovery of cysteamine bitartrate at LOQ should be in the range 80 – 120%.

LOQ confirmation

The LOQ was confirmed at the calculated LOQ concentration, acceptance criteria of LOQ/LOD or 0.05%, whichever is the highest.

Solution preparation

A solution will be prepared at the appropriate concentration.

Analysis and acceptance criteria

The solution will be injected six times, bracketed by standard injections. The RSD for peak area and the mean signal: noise ratio and recovery calculated.

- The RSD for peak area should be ≤10%.
- The mean recovery should be in the range 80 - 120%.
- The mean signal-to-noise ratio should be ≥10.

Results

Estimation

The baseline noise was determined from injections of the diluent. The S/N ratio was calculated for the 0.02 – 1.00% solutions and plotted against concentration. **Table and Figure** below. From the linear equation, the LOD (S:N = 3) was estimated as 0.170 µg/mL or 0.01% of the working concentration, the LOQ (S:N = 10) was estimated as 0.398 µg/mL or 0.03% of the working concentration.

The recovery of the solution at estimated LOQ level was in the acceptable range, 80 -120%.

Table: Sensitivity estimation

Target (%)	[Cysteamine bitartrate] (µg/mL)	Peak height (mAU)	Signal:Noise[1] (mAU)	Recovery[2] (%)
0.02	0.303	0.124	9	83.3
0.05	0.758	0.310	21	87.0
0.10	1.516	0.616	43	85.3
0.20	3.033	1.309	91	93.4
0.50	7.582	3.329	231	95.4
1.00	15.164	6.714	466	96.1

[1]Peak height divided by baseline noise; [2]Calculated against a qualified reference standard.

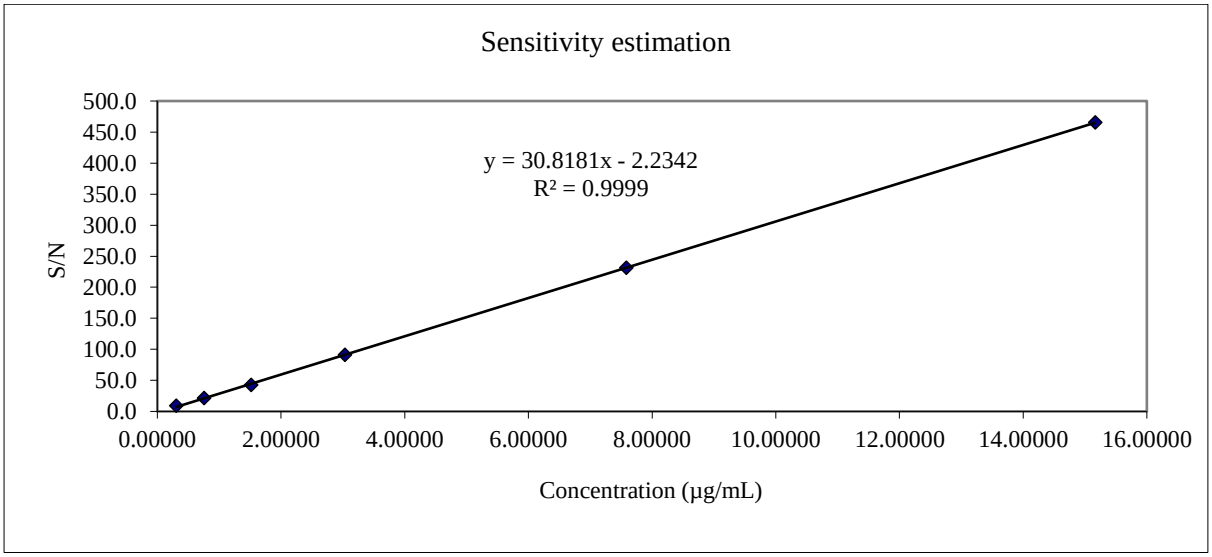


Figure: Linearity of response of signal to noise versus cysteamine bitartrate concentration, 0.02 - 1.00%

LOQ confirmation

Although LOQ was calculated to be 0.03% using a linear regression, a reporting limit of 0.05% is sufficient for drug product analysis, therefore the LOQ was confirmed at this level. A solution was prepared at 0.05% of the working concentration and injected six times.

The peak area RSD was ≤10% as required, **Table** below. The signal:noise ratio was consistently ≥10. The recoveries were outwith the acceptable range of 80 -120%. This is not uncommon for analysis at low concentrations. As peak area precision and signal to noise comply with the set criteria, accurate quantitation of peaks at this level has been proven and so the LOQ is set at 0.05%.

Table: LOW confirmation, 0.05%

Injection	Peak area (mAU/min)	Peak height (mAU)	Signal:Noise (mAU)	Recovery (%)
1	0.035	0.201	21	87.4
2	0.030	0.270	19	75.8
3	0.033	0.284	20	83.3
4	0.033	0.281	19	82.5
5	0.029	0.261	18	73.8
6	0.030	0.272	19	74.9
Average	0.032	0.278	19	79.6
%RSD	6.9	5.0	N/A	6.3

ROBUSTNESS

1. Stability of solutions

The solution stability was determined by analysing standard and drug product solutions at the nominal working concentration, 1.5 mg/mL.

Solution preparation

Standard and drug product solutions prepared for precision analysis may be used.

The solutions were stored in clear and amber glass at ambient temperature, in clear glass at 2 - 8°C and on the autosampler in the original HPLC vial. Solutions were tested at 0, 1 and 3 days against freshly prepared standard solutions.

Analysis and acceptance criteria

Standard solutions were considered stable if:

- The cysteamine bitartrate concentration of the standard solution is within 98.0 – 102.0 % of the initial (T = 0) value.

Drug product solutions were considered stable if:

- The cysteamine bitartrate concentration of the sample solution is within 98.0 – 102.0% of the initial (T = 0) value.
- No reportable related substance in the sample solutions has changed by more than 0.10% over the duration of the study.
- No new related substances greater than 0.10% are observed over the duration of the study.

Results

Standard solutions were stable for up to 3 days when stored refrigerated with recoveries within the acceptable range, 98.0 - 102.0% of initial result, **Table** below.

Table: Standard solution stability

Conditions	T = 0		T = 1 day		T = 3 days	
	Assay (mg/mL)	Recovery[1] (%)	Assay (mg/mL)	Recovery[1] (%)	Assay (mg/mL)	Recovery[1] (%)
Autosampler	1.508	-	1.505	99.8	1.462	96.9
2 - 8°C	1.508	-	1.511	100.2	1.502	99.5
Ambient clear	1.508	-	1.493	99.0	1.410	93.5
Ambient Amber	1.508	-	1.474	97.7	1.356	89.9

[1]*As a percent of the initial (T =0) result.*

Drug product solution assay values were stable for up to 3 days when stored refrigerated and at ambient clear with recoveries within the acceptable range, 98.0 - 102.0% of initial result, **Table** below.

Table: Drug product solution stability, assay

Conditions	T = 0		T = 1 day		T = 3 days	
	Assay (mg/mL)	Recovery[1] (%)	Assay (mg/mL)	Recovery[1] (%)	Assay (mg/mL)	Recovery[1] (%)
Autosampler	201.872	-	199.286	98.7	199.183	98.9
2 - 8°C	201.872	-	201.058	99.6	201.245	99.8
Ambient clear	201.872	-	201.221	99.7	200.275	99.2
Ambient Amber	201.872	-	199.179	98.7	196.752	97.6

[1]*As a percent of the initial (T =0) result.*

Table: Drug product solution stability, related substances

RRT	Storage condition (area%) and Time point				
	T = 0	Autosampler	Refrigerated	Ambient	
		Day 3	Day 3	Clear Day 3	Amber Day 3
RRT 0.72	0.04	0.04	0.04	0.04	0.04
RRT 0.73	0.05	0.04	0.04	0.05	0.04
RRT 1.18	0.02	0.02	0.03	0.03	0.02
RRT 1.32	0.03	0.05	0.04	0.04	0.03
RRT 1.57	0.03	0.03	0.03	0.03	0.03
RRT 3.49	0.12	0.13	0.14	0.13	0.12
RRT 3.71	0.03	0.02	0.02	0.02	0.02
Cystamine (base)	1.85	3.14	1.95	2.15	4.30
Total*	**2.02**	**3.32**	**2.09**	**2.32**	**4.42**

**Sum of related substance ≥0.05%, totals taken from chromatographic software.*

Based on the above data, **Table** above, both the standard and sample solutions are stable when stored for up to 3 days when stored at refrigerated conditions.

The autosampler standard and sample were both stored in amber vials for the duration of the solution stability study and the refrigerated standard and sample were both stored in clear glassware. Based on the autosampler being set at 2-8°C for analysis, it was unexpected that the cystamine (base) % rel area was significantly higher in comparison to the refrigerated data.

When assessing the ambient clear data versus the ambient amber data, it appears the ambient glassware is having an effect on the cystamine (base) impurity as the % rel area of this impurity is significantly higher in the ambient amber glassware in comparison to the ambient clear, this would explain why the cystamine (base) in the autosampler samples is significantly higher than in the refrigerated. As highlighted in **Section 'Investigation' at the end of this section (Page = 148)**], throughout the validation there has been some variation in the cystamine (base) impurity however, based on the Day 1-3 solution stability related substances data, the cystamine (base) is significantly increasing at each of the timepoints for the autosampler sample therefore, the unexpected higher % rel area is not related to the variability between vials.

2. Intermediate precision

Intermediate precision was determined by a second analyst performing the method reproducibility test as described in section 'precision'. The analysis was performed on a different day using different standard and sample preparations (same sample batch as used for method reproducibility test), different instrument and different column.

Solution preparation

Prepare six drug product samples as above (drug product solution).

Analysis and acceptance criteria

The mean, SD, %RSD and 95% confidence interval were calculated and reported. The results assessed against the following acceptance criteria:

- The %RSD for drug product content should be ≤2.0%.
- The %RSD for individual related substances ≥0.05 but <0.2% should be ≤20%.
- The %RSD for individual related substances ≥0.2% should be ≤10%.
- The %RSD for the total related substances should be ≤5%.

Additionally, the assay and related substances data from each analysis will be compared and assessed against the following acceptance criteria:

The % difference for drug product content between the laboratories should be ≤2.0%.

- The absolute area% difference for individual related substances should be ≤0.1%.
- The absolute area % difference for total related substances should be ≤0.2%.

The mean, SD, %RSD and 95% confidence interval (n = 12) were also calculated and reported.

Results

The %RSD for cysteamine bitartrate content of the six preparations was ≤2.0% as required, **Table** below.

Table: Intermediate precision, assay

Details	Content (mg/mL)
Preparation 1	200.360
Preparation 2	200.457
Preparation 3	199.084
Preparation 4	200.292
Preparation 5	199.726
Preparation 6	200.012
Mean (n=6)	199.989
RSD (n=6)	0.3

All detected related substances are shown in **Table** below. For related substances ≥0.2%, RSD was ≤5%. For related substances ≥0.05 and <0.2%, RSD failed the criteria of ≤10%. The RSD for total related substances failed the criteria of ≤5%.

Table: Intermediate precision, Related substances area %

RRT	Rel Area %						Mean	%RSD
	1	2	3	4	5	6		
RRT 0.72	ND	ND	ND	ND	ND	ND	N/A	N/A
RRT 0.73	ND	ND	ND	ND	ND	ND	N/A	N/A
RRT 0.85	0.02	0.02	0.02	0.02	0.02	0.02	<LOQ	4
RRT 1.11	0.05	0.04	0.04	0.04	0.04	0.04	<LOQ	8
RRT 1.18	0.06	0.05	0.06	0.06	0.06	0.06	0.06	2
RRT 1.32	0.05	0.05	0.05	0.05	0.05	0.04	0.05	4
RRT 1.57	0.03	0.03	0.03	0.03	0.03	0.03	<LOQ	4
RRT 3.49	0.12	0.12	0.12	0.13	0.12	0.13	0.12	3
RRT 3.71	0.03	0.03	0.03	0.03	0.03	0.03	<LOQ	3
Cystamine (base)	1.82	2.40	2.29	1.83	2.23	1.84	2.07	13
Total*	**2.09**	**2.63**	**2.52**	**2.06**	**2.46**	**2.02**	**2.30**	**12**

**Sum of related substance ≥0.05%, totals taken from chromatographic software.*

The % difference for the cysteamine bitartrate content of the twelve preparations between laboratories was ≤2.0%, **Table** below.

Table: Precision (n=12) (Performed at AMRI development and Quality Control departments)

Details		Content (mg/mL)
	Preparation 1	201.872
	Preparation 2	201.964
	Preparation 3	201.261
	Preparation 4	202.106
	Preparation 5	201.584
	Preparation 6	201.402
	Preparation 1	200.360
	Preparation 2	200.457
	Preparation 3	199.084
	Preparation 4	200.292
	Preparation 5	199.726
	Preparation 6	200.012
% Difference between analysts		0.9
Mean		200.843
SD		1.0
RSD		0.5

All detected related substances are shown in **Table** below for the twelve preparations. The absolute area% difference for related substances was ≤0.1% with the exception of the cystamine (base). The absolute area% difference for total related substances failed the criteria of ≤0.2%, this is due to the variability in cystamine (base) from vial to vial [**See Section Investigation: Variation in cystamine (base) between vials at the end of this section (Page = 153)**].

Table: Precision for related substances (n=12) (Performed at AMRI development & Quality Control departments)

RRT	Drug product preparation (area %) – Analyst 1							Drug product preparation (area %) – Analyst 2							%Diff.
	1	2	3	4	5	6	Mean	1	2	3	4	5	6	Mean	
RRT 0.72	0.04	0.05	0.05	0.05	0.04	0.04	0.05	ND	ND	ND	ND	ND	ND	N/A	N/A
RRT 0.73	0.05	0.05	0.05	0.05	0.05	0.05	0.05	ND	ND	ND	ND	ND	ND	N/A	N/A
RRT 0.84	ND	ND	ND	ND	ND	ND	N/A	0.02	0.02	0.02	0.02	0.02	0.02	0.02	N/A
RRT 1.11	ND	ND	ND	ND	ND	ND	N/A	0.05	0.04	0.04	0.04	0.04	0.04	0.04	N/A
RRT 1.18	0.02	0.02	0.03	0.02	0.02	0.02	0.02	0.06	0.05	0.06	0.06	0.06	0.06	0.06	0.04
RRT 1.32	0.03	0.04	0.03	0.03	0.03	0.03	0.03	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.02
RRT 1.57	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.00
RRT 3.49	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.13	0.12	0.13	0.12	0.00
RRT 3.71	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.00
Cystamine (base)	1.85	1.87	1.68	1.84	1.66	1.98	1.81	1.82	2.40	2.29	1.83	2.23	1.84	2.07	0.26
Total*	**2.17**	**2.21**	**2.02**	**2.17**	**1.98**	**2.30**	**2.14**	**2.18**	**2.74**	**2.64**	**2.19**	**2.58**	**2.19**	**2.42**	**0.25**

Conclusion

The method was successfully validated with the exception detailed below in the **'deviations in validation protocol**'.

Based on the findings of the validation exercise, the injection sequence shown in **Table** below is recommended for routine use of the method.

Table: Recommended sample sequence for routine use of method

Sequence	Solution	Number of injections
1	Blank (diluent)	Until stable baseline, free from interfering peaks is obtained
2	LOQ	1
3	Standard 1	6
4	Standard 2	2
7	Sample 1	1
8	Sample 2	1
9	Sample….[1]	1
10	Standard	1

[1]*Bracketing standard injections (single) should be performed after every 10 sample injections and at the end of the sequence.*

The system suitability criteria shown in **Table** below should be met before sample analysis.

Recommended system suitability criteria for routine use of method

Solution	System suitability parameter	Nominal acceptance criteria
Blank solution	Specificity	Absence of interfering peaks
Standard 1 solution (6 consecutive injections)	Retention time (main peak) precision	%RSD ≤2.0%
	Peak area (main peak) precision	%RSD ≤2.0%
Resolution	Plate count (EP)	Record
	Peak asymmetry (EP)	Record
Standard 2 (duplicate injections)	Standard agreement = $\frac{\text{Area Std 2}}{\text{Area Std 1}} \times \frac{\text{Weight Std 1}}{\text{Weight Std 2}} \times 100$	100 ± 2.0%
Standard 2 (all injections throughout run)	Retention time and peak area precision	%RSD ≤2.0%

Sterility Test Method Validation

Albany Molecular Research Inc. (Glasgow) Limited validated the pharmacopeia sterility test method using samples of drug product manufactured in the development technical or clinical batch. Validation and testing were outsourced to an approved AMRI sub-contractor.

Bacterial Endotoxins Test Method Validation

AMRI Glasgow validated the pharmacopeia bacterial endotoxins test method using samples of drug product manufactured in the development technical or clinical batch. Testing was conducted by AMRI Glasgow Microbiology department.

Summary of validation results

The data on the parameters for validation of the analytical methods, the acceptance limits and the results are provided in the **Table** below.

Parameter	**Acceptance criteria**	**Results**
System suitability 1. Specificity 2. Cysteamine bitartrate RT precision (S1, n=6) 3. Cysteamine bitartrate peak area precision (S1, n=6) 4. Cysteamine bitartrate peak asymmetry (EP) 5. Cysteamine bitartrate theoretical plate count (EP) 6. Standard agreement	1. Blank free from interfering peaks 2. RSD≤2.0% 3. RSD≤2.0% 4. Record 5. Record 6. 100 ± 2.0%	1. PASS 2. 0.0 – 0.1% 3. 0.3 – 0.5% 4. 1.6 -1.8 5. 10986 6. 99.4 - 100.3%
Specificity	1. Cysteamine bitartrate peak should have no significant interference from sample diluent or related substances/degradants. 2. Related substances should be sufficiently resolved from each other and from cysteamine bitartrate to allow accurate and reproducible integration. 3. Cysteamine bitartrate peak purity for degraded solutions should be comparable to non-degraded solution	1. PASS 2. PASS 3. PASS
Linearity 1. Assay level (60-140%) 2. Cysteamine bitartrate Related Substance level (0.02-1.0%)	1. R≥0.999 2. R≥0.99	1. 1.000 2. 1.00
Precision (method repeatability)	1. %RSD for assay/recovery (n=6) for drug product 2. %RSD for individual related substances ≥0.05 but <0.2% (area%) should be ≤20% 3. %RSD for individual related substances ≥0.2% should be ≤10% 4. The %RSD for the total related substances should be ≤5%	1. 0.2% 2. 2-6% 3. 6% 4. 6%

Intermediate precision	1. The % difference for drug product content between the laboratories should be ≤2.0% 2. The absolute area% difference for individual related substances should be ≤0.1% 3. The absolute area% difference for total related substances should be ≤0.2%	1. 0.5 2. 0.02-0.26%* 3. 0.25%*
Accuracy	1. Each individual recovery (n=9) should be 98.0-102.0% of theory 2. %RSD of the recovery (n=3) at each concentration level should be ≤2.0% 3. Accuracy (n=9)	1. 99.7-100.7% 2. 0.1-0.4% 3. 100.4%
Sensitivity 1. Estimation 2. Confirmation	1. LOD (signal:noise =3): report result LOQ (signal:noise =10): report result 2. %RSD for LOQ peak area should be ≤10% Mean recovery (n=6) should be 80-120% (LOQ confirmed at 0.05% of working conc) Mean signal to noise	1. 0.01% 0.03% 2. 6.9% 79.6%* 19
1. Solution stability	Standard solutions were stable if: 1. Cysteamine bitartrate concentration was within 98.0 - 102.0% of the initial value. Drug product solutions were stable if: 1. Cysteamine bitartrate concentration was within 98.0 – 102.0% of the initial value. 2. No related substance ≥0.05% (by area) had increased by >0.10% from the initial value. 3. No new related substance ≥0.10% was detected in the aged solutions which were not present at initial.	Standard solutions were stable for up to 3 days when stored at 2-8°C in clear glassware. Drug product solutions were stable for up to 3 days when stored at 2-8°C in clear glassware.

**Refer to comment in the deviations of the validation protocol below (page = 148).*

DEVIATIONS IN THE VALIDATION PROTOCOL

Deviations made from the validation protocol are detailed below. However, the deviations had no impact on the validity of the data.

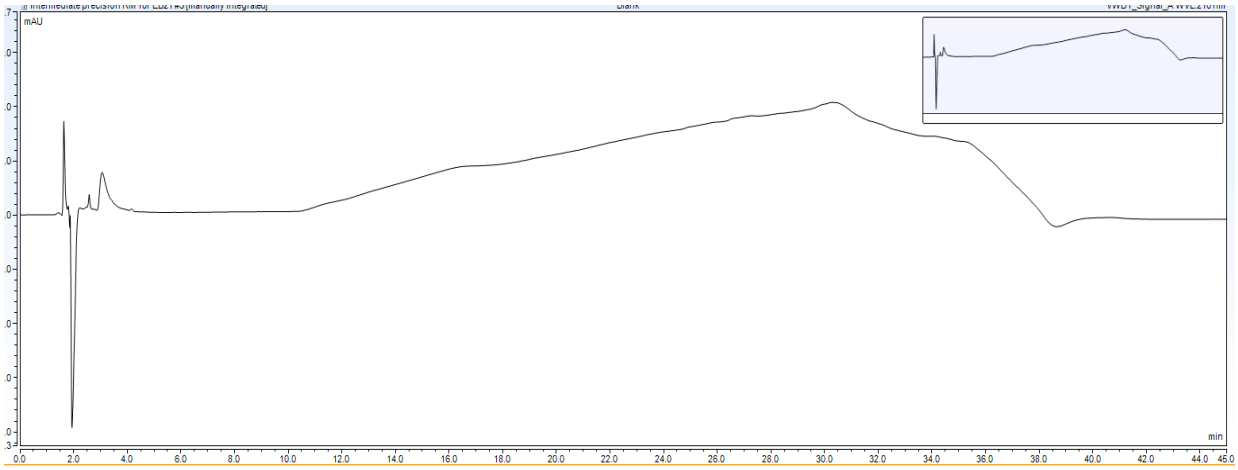
- The %RSD for total related substances in the Precision and Intermediate Precision sections fail to meet the criteria of ≤5%. This is due to the variability in cystamine (base) between vials.
- The absolute area % difference for individual related substances and total related substances during the intermediate precision analysis fails the criteria of ≤0.1% and ≤0.2% respectively. This is due to the variability of cystamine (base) between vials (**Note Investigations below**).
- The recoveries of the LOQ confirmation injections were outwith the typical criteria of 80-120%.
- No peak match data obtained for heat stressed samples at the 24-hour timepoint due to 24 hours samples discarded in error prior to retest (**Note Investigations below**).

INVESTIGATIONS

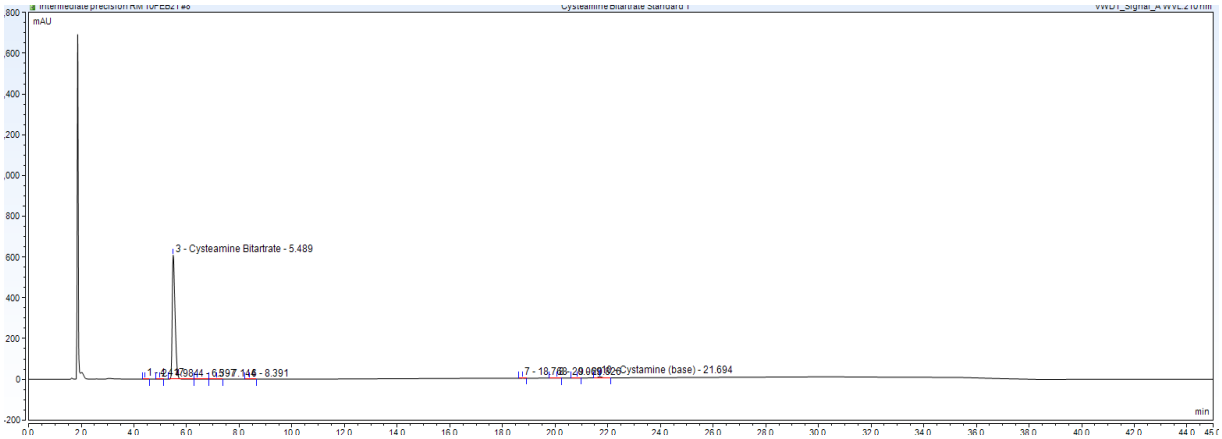
Investigation: Specificity

The chromatography achieved for the initial specificity analysis analysed on the DAD detector was atypical, (**See Figure below: Placebo solution chromatogram**), this issue was also observed during another study with this product prior to the specificity samples being analysed on both the DAD and UV detectors. Initially, based on the chromatography achieved during the other study, it was thought that the reason for the atypical chromatography was down to the stability of the product however, based on the specificity data, this was proven not to be the root cause. For the specificity analysis, the same stressed solutions were run on two separate systems, one with a UV detector and one with a DAD detector along with different batches of mobile phase and column.

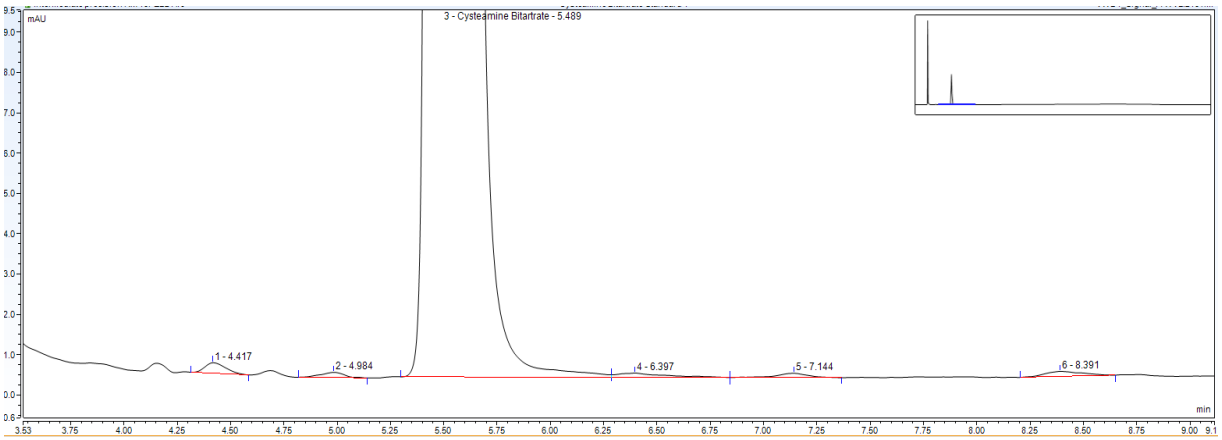
The chromatography obtained for the sample solutions rand on the UV detector was typical (**See Figure below: Example diluent chromatogram**), and chromatography obtained for the same sample solutions on the DAD detector was atypical, [**See Figure below: Example standard chromatogram (zoomed in)**]. To add, the atypical chromatography obtained on the DAD detector and with what was seen in the previous study, it was only the samples which were impacted, and the chromatography obtained for the standard solutions were typical.



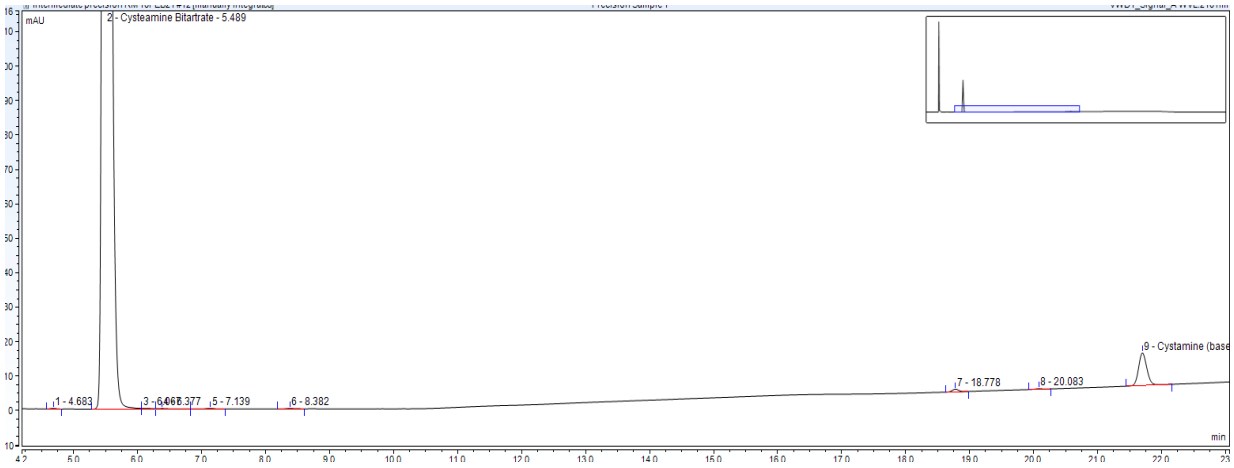
Example diluent chromatogram



Example standard chromatogram



Example standard chromatogram (zoomed in)



Example sample chromatogram

As it was only the sample solutions which were impacted, to investigate this atypical chromatography further, the pH of the standard solution was analysed to determine if the pH of the standard and sample is comparable.

It was determined that the pH of the standard solution was pH 3.7 and the pH of the sample solution was pH 5.8. Therefore, due to the standard solution being more acidic than the sample solution, there was a possibility that there could have been an issue with the mixing of mobile phase A and mobile phase B. This potential root cause was determined based on the fact that the pH of the standard was more acidic than the sample material, if more of the acidic mobile phase A was being introduced and causing the pH of the sample to drop to the same as the standard then this could potentially have impacted the chromatography of the sample only with no effect on the standard material. This atypical chromatography observed during the specificity section was the only time throughout the validation that this issue was observed, therefore there was no reason to suggest that it was related to column performance or method related.

The specificity samples were re-prepared from the stressed sample stock solutions and re-analysed (**See Figure above: Example standard chromatogram**) on the same system with the same column along with the investigational samples. Due to the samples being re-analysed, the 24 h samples had been disposed of in error therefore only the heat stressed sample (1 week) and heat stressed sample (2 weeks) were re-analysed (Deviation from the validation protocol NVB-P-01-02).

On the re-analysis of the stressed samples on the DAD detector, typical chromatography was achieved. However, peak match is not >950 indicating there is a possibility of co-elution of a related substance. However, for the forced degradation samples, the peak match is not reduced indicating that if there is any co-elution it is not from a degradation product and

therefore the method can still be considered stability indicating (Deviation from the validation protocol NVB-P-01-02).

For the investigational work, the light stressed (uncovered) sample was used and the pH of the sample was altered using mobile phase A. The pH of the sample was altered to various pHs within the range of pH 4.9 - 2.7, this covered pHs between the standard and sample and below the standard. On review, all chromatography achieved for the samples at the different pH values was typical. The conclusion drawn from the investigational work was, as the pH of the sample decreases, the area of the sample also decreases however the resolution of the main peak is unaffected [**See Figure above: Example standard chromatogram (zoomed in)**].

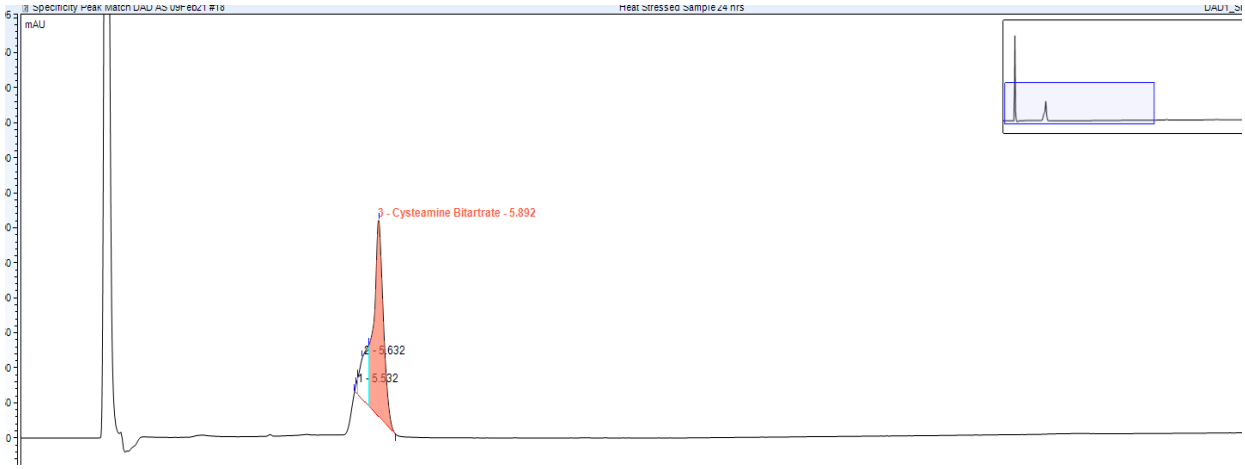


Figure: 24hr heat stressed sample, DAD detector

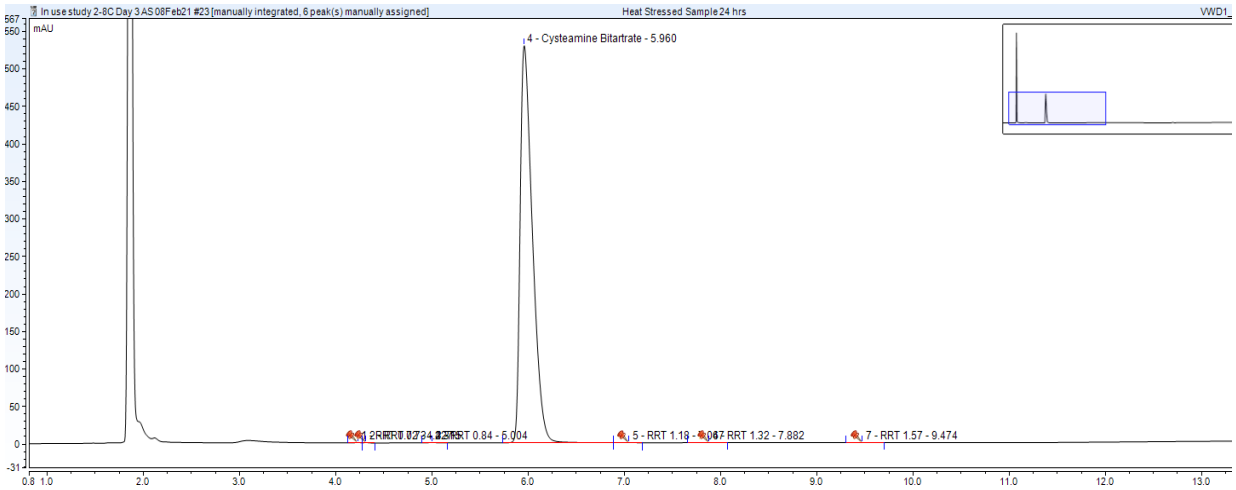


Figure: 24hr heat stressed sample, UV detector

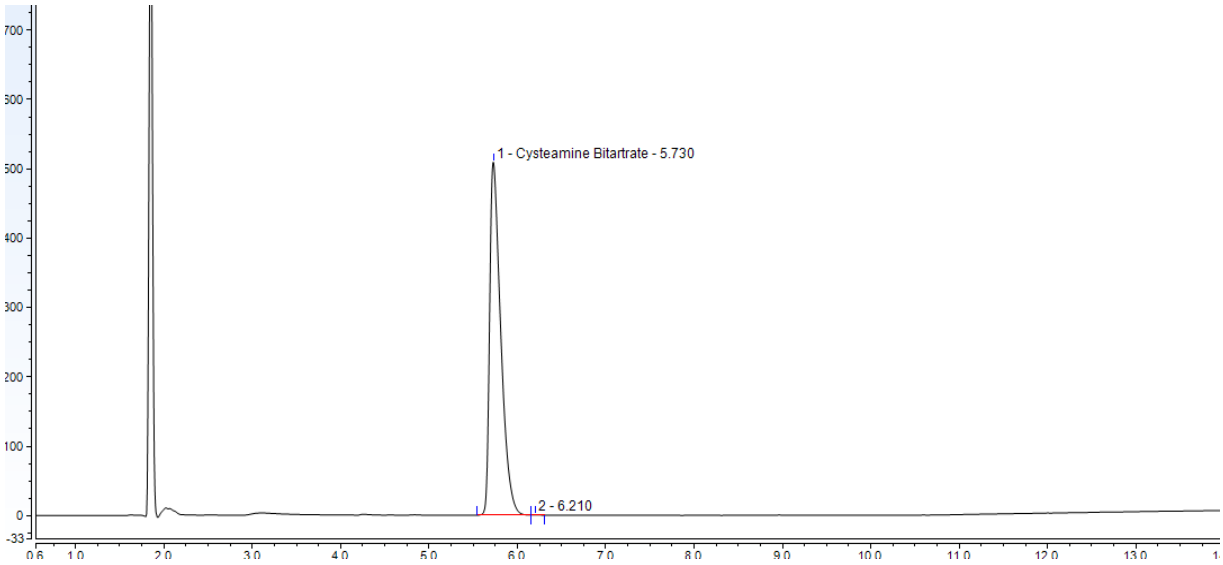


Figure: Re-prepared 1 week heat stressed sample, DAD detector

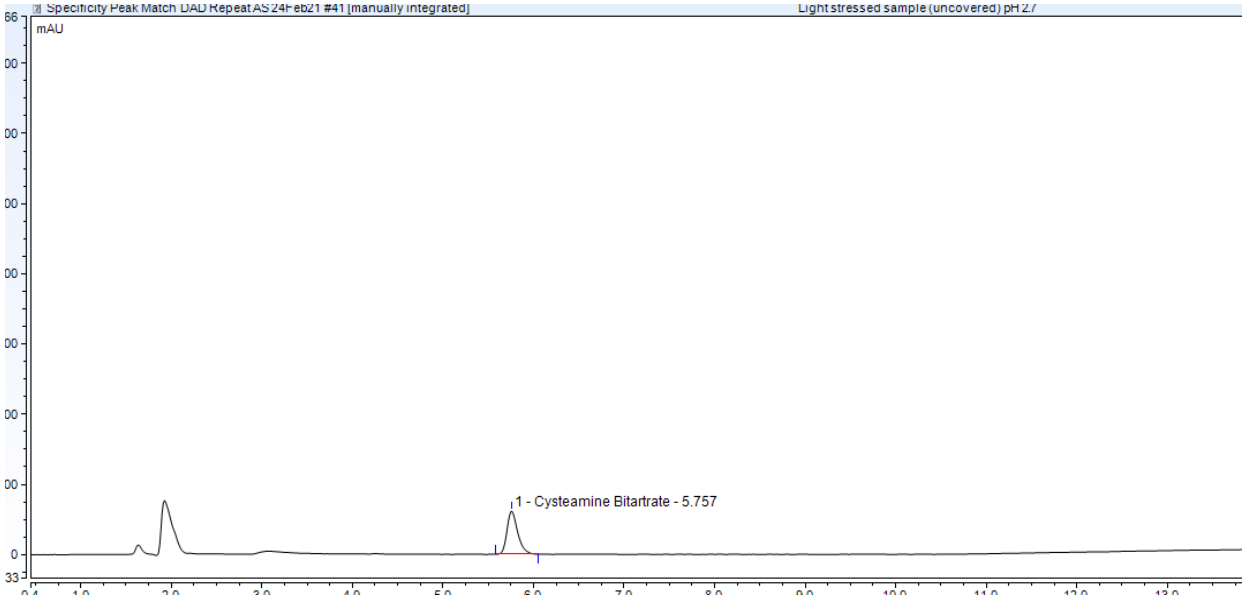


Figure: Light stressed (uncovered) investigational sample, pH 2.7

As the atypical chromatography was only obtained during one section of the validation and could not be replicated with altering the pH of the sample, we are unable to draw a conclusion and establish a root cause for the atypical chromatography at this stage. All materials and reagents were compared across all studies for this product and there is no significant difference between column, materials or specifics used when the issue has been observed. The issue was investigated and will be further highlighted if obtained in future analysis for this product.

Investigation: Variation in cystamine (base) between vials

Throughout the validation, it was observed that there was variability between vials for the cystamine (base) impurity. This was first highlighted during the precision analysis as the %RSD for total related substances failed the specification of ≤5%. As all other impurities obtained during the precision analysis were within specification for %RSD, the variable % rel area of the cystamine (base) resulted in the total related substances failing the criteria, (Deviation from the validation protocol NVB-P- 01-02).

Similarly, during the intermediate precision analysis and the specificity analysis, variability in the cystamine (base) between vials was observed resulting in criteria not being met, (Deviation from the validation protocol NVB-P-01-02).

On review of the technical batch in storage at -20°C, it was observed that after ~8 months storage, not all vials had frozen and that drug product in various vials was still in solution. This highlighted that the rate of the drug product freezing was variable across the batch potentially resulting in variability in impurity data which would explain the reason for the variable results seen across the validation.

To investigate this further and determine the root cause of the variability in cystamine (base), the intermediate precision sample 1 was re-analysed and one of the un-frozen vials from the technical batch storage was analysed, the impurity data from both the frozen (precision sample 1) and the un- frozen vial was then compared.

The impurity data obtained from the intermediate precision sample 1 re-analysis was comparable to the results from the intermediate precision analysis and there was an increase in the % rel area of cystamine (base) for the un-frozen vial, (**See Table below**).

Table: Related substances frozen v un-frozen vial

RRT	Rel Area %		
	Intermediate Precision Sample 1: Initial	Intermediate Precision Sample 1: Re-analysis	001/NVB/20: Un-frozen vial
RRT 0.85	0.02	0.02	0.02
RRT 1.11	0.05	0.02	0.04
RRT 1.18	0.06	0.02	0.02
RRT 1.32	0.05	0.04	0.03
RRT 1.57	0.03	0.03	0.03
RRT 3.49	0.12	0.07	0.09
RRT 3.71	0.03	0.02	0.02
Cystamine (base)	1.82	2.09	2.69
Total*	**2.10**	**2.16**	**2.78**

**Sum of related substances ≥0.05%.*

From the data above, this concludes the initial root cause for the variable results seen with the cystamine (base) impurity only is due to the variation in freezing rate for each of the vials across the technical batch.

2.1.P.4.4 Batch analyses

The following batches were produced and used for different purposes:

Formulation composition	Batch Number	Batch size	Manufacturing date	Primary packaging	Use of the batch
Final formulation (non-GMP batch)	001/NVB/20	500 vials	May 2020	Type I, 2 mL clear glass vias (Schott: VC002-13C)	Analytical testing/supportive stability data
GMP batch	P04620	7,000 vials	Dec 2020		Clinical Batch/ongoing stability

The stability data of the non-GMP and GMP batches indicated above are detailed in **Section 2.1.P.8.**

CoA for the batch release of GMP batch # P04620 is provided below.

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CERTIFICATE OF ANALYSIS

Product:	Cysteamine Bitartrate 200mg/mL Solution
BMR Number:	NVBP07
Batch Number:	P04620
Date of Manufacture:	22 Dec 20
Storage Conditions:	-20°C
Testing Reference:	Logbook QLB3046 pg 11-41 AMRI Endotoxin Report: 9310011f-203d-432e-84c9-0911aa3f5c85 AMRI Sub Visible Particulates Report Charles River Sterility Report: 193132
Certificate Number:	CA/038/21 v02
Project:	15087

The following results are for the Release testing of NVBP07 P04620. The results are reported as detailed in the Test Details Document AS316v02.

Test	Test Site	Method	Specification	Result		Pass /Fail
Appearance	AMRI	Visual, C/TE/8257	Clear solution – colourless. Free from visible particles	Clear solution, colourless. Free from visible particles		Pass
pH	AMRI	C/EQ/8007, pH Eur 2.2.3, USP<785>	Report results	pH 5.5		Reported
Osmolality	AMRI	C/EQ/8009, Ph Eur 2.2.35, USP<785>	Report results	219 mOsm/kg		Reported
Extractable Volume	AMRI	C/GE/8516, Ph Eur 2.9.17, USP<697>	NLT 2.2mL	2.4 mL		Pass
Identification (Retention time)	AMRI	QCP003, HPLC[A]	Retention time compares to the reference standard	Retention time compares to the reference standard		Pass
Assay	AMRI	QCP003, HPLC[A]	95..0 – 105.0% Release 90.0 – 105.0 % Shelf-life	100.8%		Pass
Purity	AMRI	QCP003, HPLC[A]	NLT 95%	95.9%		Pass
Impurities	AMRI	QCP003, HPLC[A]	Cystamine (Base): ≤ 5.0% Any single unknown impurity: ≤0.15% Total unknown impurities: ≤0.5% Total impurities: ≤5.0%	**RRT**	**%Area**	Pass
				1.13	0.09	
				1.32	0.05	
				1.57	0.05	
				3.49	0.05	
				Cystamine (Base)	3.90	
				Total	**4.14**	

[A]testing carried out under change control CR-09828, using assay undergoing validation concurrently with the release testing

Results compiled and verified by : *Ashleigh Bell, QC Analyst II* ABell	Date: 29 Apr 21
Results comply with specification : *Graeme Anderson, QC Investigation Specialist* G. A	Date: 29 Apr 21

C.GE.8504.09 Page 1 of 2

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CERTIFICATE OF ANALYSIS

Product:	Cysteamine Bitartrate 200mg/mL Solution
BMR Number:	NVBP07
Batch Number:	P04620
Date of Manufacture:	22 Dec 20
Storage Conditions:	-20°C
Testing Reference:	Logbook QLB3046 pg 11-41 AMRI Endotoxin Report: 9310011f-203d-432e-84c9-0911aa3f5c85 AMRI Sub Visible Particulates Report Charles River Sterility Report: 193132
Certificate Number:	CA/038/21 v02
Project:	15087

Test	Test Site	Method	Specification	Result	Pass /Fail
Identification (DAD Spectra)	AMRI	QCP003, HPLC[A]	λ max in the reference solution and in the sample solution are the same within ±3nm	λ max in the reference solution and in the sample solution are the same within ±3nm	Pass
Particulate matter	AMRI	C/EQ/8042, Ph Eur 2.9.19 Method I, USP<788> Method I	Complies with Ph. Eur./USP	10µm: 1493 particles per container 25µm: 44 particles per container	Pass
Endotoxins	AMRI	M/TE/5273, Ph Eur 2.6.14, USP<85>	NMT 10 EU/mL	<2 EU/mL	Pass
Sterility	Charles River	Ph Eur 2.6.1, USP<71>	Sterile	Sterile	Pass

[A]testing carried out under change control CR-09828, using assay undergoing validation concurrently with the release testing
Sub contract testing performed by:
Charles River Laboratories Ireland Ltd, Carrentrila, Ballin,. Co. Mayo, F26 A786, 353 96 20800

Version History
Version 01: New issue
Version 02: Addition of purity assay

Results compiled and verified by : *Ashleigh Bell, QC Analyst II*	Date: 29 Apr 21
Results comply with specification : *Graeme Anderson, QC Investigation Specialist*	Date: 29 Apr 21

C.GE.8504.09 Page 2 of 2

The GMP certificate for the GMP batch # P04620 is provided below.

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AMRI Certificate 3	**Batch Completion**			
Company	**NovaBiotics**			
Product	**Cysteamine 200mg/mL solution**			
Item Master No.	**GFGD0062**			
Dosage form	**Liquid fill**			
Package size	**2mL clear glass vials**			
Batch Number	**P04620**		BMR Number	**NVBP07**
Certification Scope	Clinical Product	☒	Pre-clinical Product	☐
	Unlabeled Product	☒*	Labelled Product	☐**

This product was manufactured at AMRI (Glasgow) Ltd., Todd Campus, Acre Road, G20 0XA under MIA(IMP) 19124 **in Non-Cytotoxic Unit 1**clean-room suites on the **22 Dec 2020.**

This batch has been manufactured and checked in accordance with the principles and guidelines of good manufacturing practice for medicinal products for human use and investigational medicinal products for human use as laid down in Commission Directive 2003/94/EC.

The product was manufactured in strict accordance with the instructions in the Batch Manufacturing Record and all sections have been reviewed by Quality Assurance. Any deviations or out of specification results have been reported.

Comments / Remarks / Additional information:
None

* This batch requires further assembly and/or QP certification before it can be used in a Clinical Trial.

** This batch has been reviewed against the following regulatory submission documents:

29 Apr 21

Martin Reid, Head of Quality, QP
Qualified Person in accordance with article 49 of EEC Directive 2001/83

2.1.P.4.5 Characterisation of impurities

No additional Impurities / known degradants observed in the IMP other than the ones already described **Section: 2.1.S.3.2: Impurities**.

2.1.P.4.6 Justification of specifications

The specification for cystamine impurity was set based on purity of cysteamine bitartrate by area% curve. This was set as 95.0 – 105.0 % for QP release and 90.0 -105.0% for shelf life based on the specifications that was set for our oral cysteamine bitartrate capsule (Lynovex) in the past and acceptable shelf-life stability (90.0 -105.0%) from the literature for the marketed Cystagon capsule.

2.1.P.5 Reference standards and materials

Refer to **Section 2.1.S.5: Reference standards and materials.**

2.1.P.6 Container closure system

The sterile IMP liquid solution was filled into 2 mL Type I glass vials (Schott). The vials were filled and purged with nitrogen after dosing and were closed with butyl rubber Flurotec coated stoppers (West) and secured with over-seals (West). The product details and specifications, and the details of the suppliers are provided below.

Adelphi Healthcare Packaging supplied vials, stoppers and over-seals to Albany Molecular Research Inc. (Glasgow) Limited [AMRI]. Container closure testing was performed in accordance to USP<1207>.

Product	**Product details**
VIAL SIZE AND TYPE	Vial – 2 mL clear (VC002-13C)
STOPPER SIZE AND TYPE	13 mm Injection Stopper Flurotec (New Generation) 4023/50 B2-40 Westar RS (WPS # 1012- 2737) INJ13TB3WSRS
OVERSEAL SIZE AND TYPE	13 mm Tear Off Overseal CETW13 WPS # 5920-2274

Specifications of vials

The material specifications and the diagram of the 2 mL clear vial (VC002-13C) are provided below.

Product details			
Item Master Number:	GCOM0003	**Status:**	Active
Description:	Vial- 2 mL clear (VC002-13C)		
Standard Expiry Period:	1460	**Storage:**	Ambient (15-25°C)
Supplier:	Schott	**Supplier Part Number:**	VC002-13C
Grade:	N/A	**Drawing reference:**	04110247

Sample requirements			
Release:	C/TE/8259 Appendix 2and3 (**See 3.1.A.1 Facilities and equipment**)	**Full Compendial:**	N/A
Retest:	NIA- Documentation/Label check only	**Retain:**	10, from QC Sample

Approval requirement			
Test 1:	Component free from visible contamination, complies with AQL limits	**Test 2:**	Refer to drawing 04110247
Test 3:	NIA	**Test 4:**	NIA
Endotoxin Level:	NIA	**Calculation of Bioburden:**	NIA

Documentation requirements			
TSE/BSE Statement:	Yes	**Certificate of Analysis/Conformity:**	Yes
Certificate of Irradiation:	No	**Certificate of Sterility:**	No
Other 1:	NIA	**Other 2:**	NIA

The frozen IMP vial with IV cysteamine bitartrate is shown in **Figure** below.

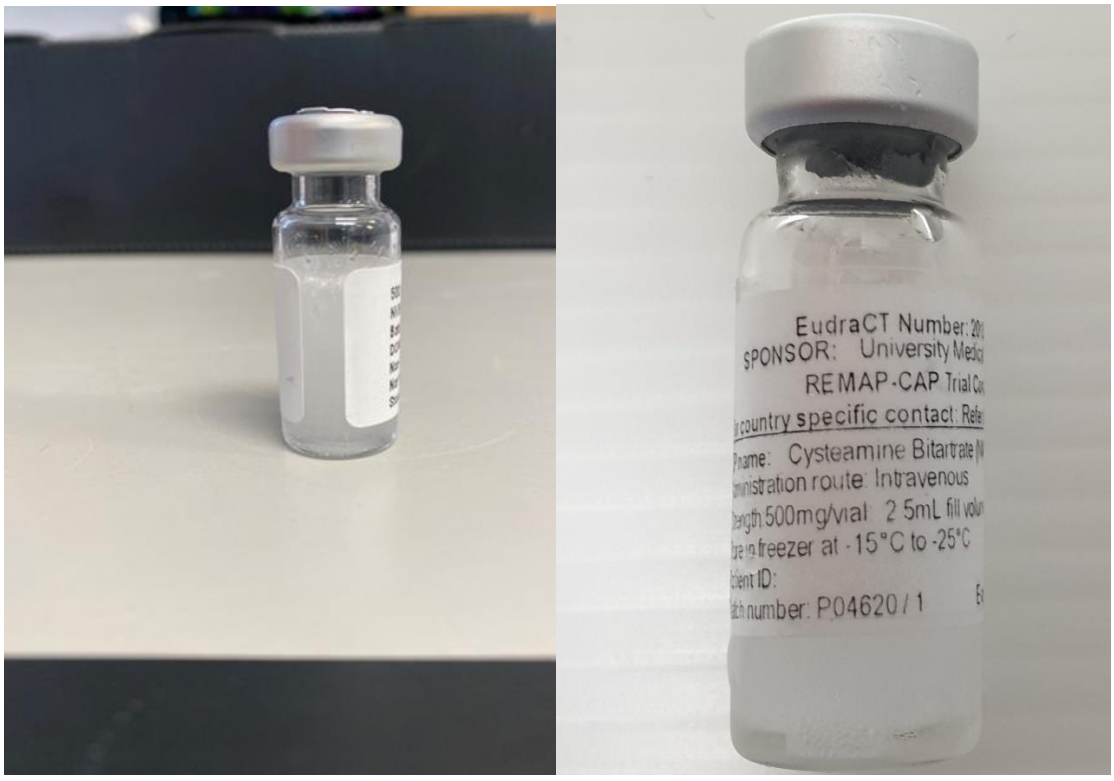
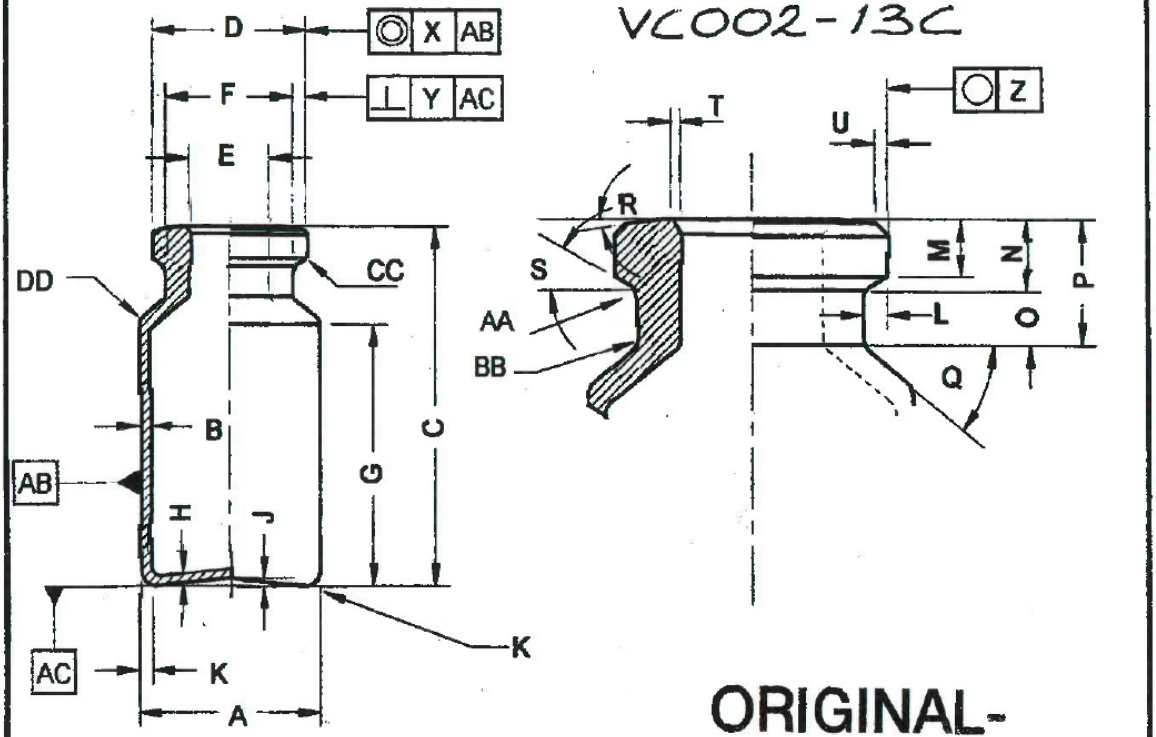


Figure: *Shows a representative frozen 2 mL IMP vial with 2.5 mL fill volume, containing cysteamine bitartrate 200 mg/mL (500 mg/vial).*

SCHOTT Schott Glaskontor	Zeichnungs Nr.: 04110247	Gez: 28.06.01 Kum Gepr: 03.07.01
Bezeichnung: 3ml Injektion	Glasart: FIO-KLAR	Kunde / Zeich. Nr.: VC002-13C Adelphi (Tubes) LTD

VC002-13C



ORIGINAL-ZEICHNUNG

Bem.:

A = 14,25 ±0,15	J = 0,7 max	R = 3° ±2°	Z =
B = 0,95 ±0,03	K = 1,5 ±0,50	S = 30° ±5°	AA=
C = 39,5 ±0,50	L =	T = 0,5 ±0,20/45°	BB=
D = 13,0 ±0,20	M = 3,6 ±0,20	U = REF 0,5/45°	CC=
E = 7,0 ±0,20	N =	V =	DD=
F = 10,5 max	O =	W =	EE=
G = 26,0 min	P = 8,0 ±0,25	X =	FF=
H = 0,7 min	Q = 30° ±5°	Y =	GG=

Änderungsgrund	Alt	Neu	Datum	Name	Index

F:\db\access\PK-Zeich\PK-zeich.mdb - Berichte:Zeichnung deutsch

Specification of stopper

The material specifications and the diagram of the injection stopper Flurotec (New Generation) are provided below.

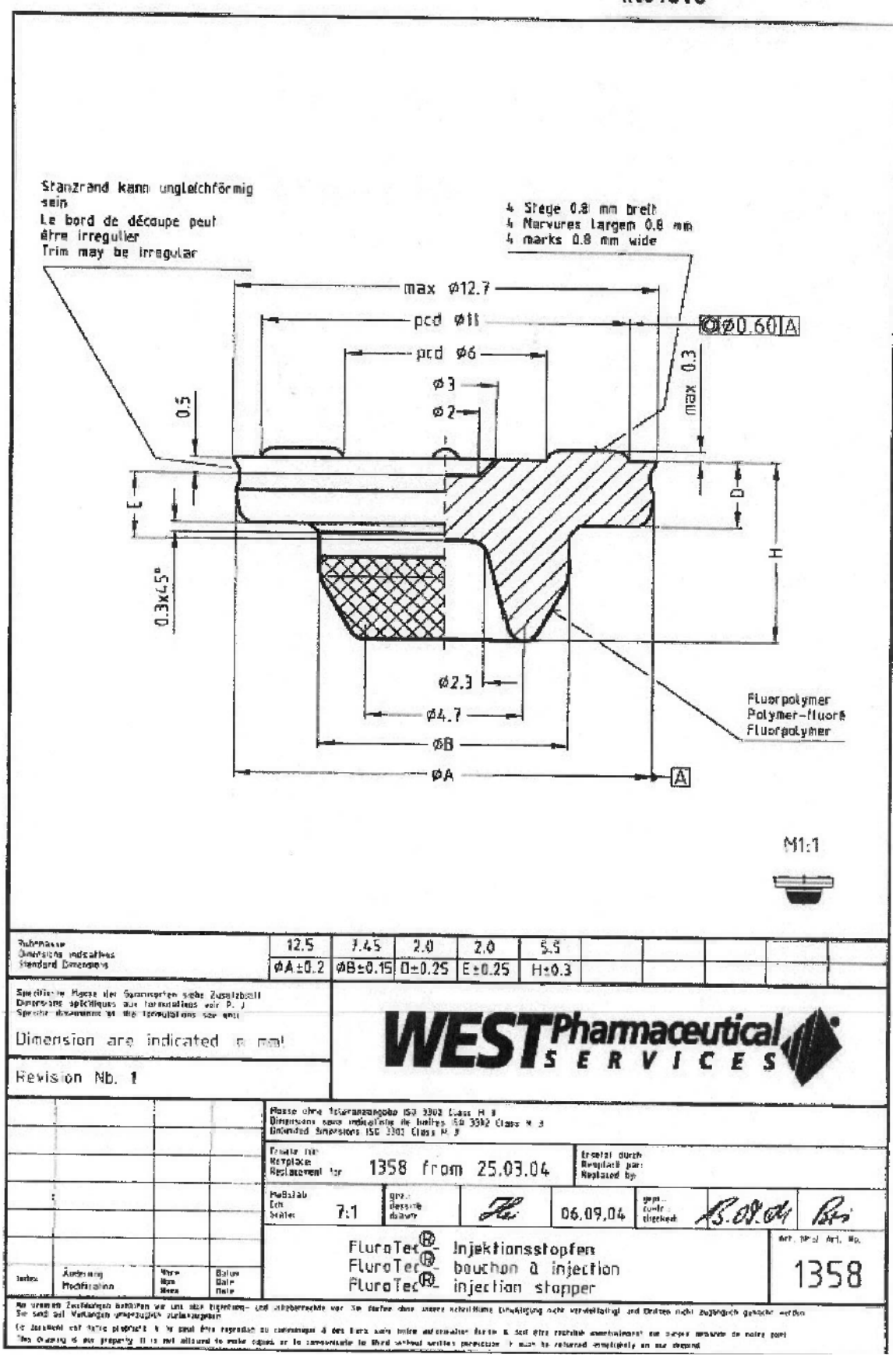
Product details			
Item Master Number:	GCOM0018	**Status:**	Active
Description:	13 mm Injection Stopper Flurotec (New Generation) 4023/50 B2-40 Westar RS (WPS# 7001-8021) INJ13TB3WRS		
Standard Expiry Period:	1460	**Storage:**	Ambient (15-25°C)
Supplier:	West Pharma	**Supplier Part Number:**	INJ13TB3WRS
Grade:	N/A	**Drawing reference:**	1358

Sample requirements			
Release:	C/TE/8259 Appendix 2and3 (**See 3.1.A.1 Facilities and equipment**)	**Full Compendial:**	N/A
Retest:	N/A- Documentation/Label check only	**Retain:**	10, from QC Sample

Approval requirement			
Test 1:	Component free from visible contamination, complies with AQL limits	**Test 2:**	Refer to drawing 1358
Test 3:	N/A	**Test 4:**	N/A
Endotoxin Level:	N/A	**Calculation of Bioburden:**	N/A

Documentation requirements			
TSE/BSE Statement:	Yes	**Certificate of Analysis/Conformity:**	Yes
Certificate of Irradiation:	No	**Certificate of Sterility:**	No
Other 1:	WFI Final Rinse	**Other 2:**	N/A

ADELPHI ITEM CODE: INJ13T3



Specifications of over-seal

The material specifications and the diagram of the tear off over-seal is provided below.

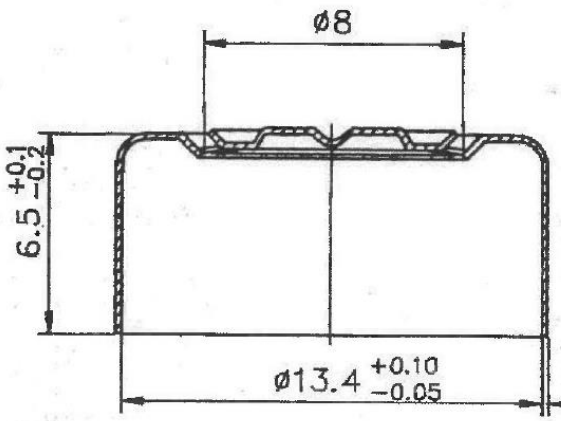
Product details			
Item Master Number:	GCOM0032	**Status:**	Active
Description:	13 mm Tear Off Overseal CETW13 WPS# 5920-2274		
Standard Expiry Period:	1460	**Storage:**	Ambient (15-25°C)
Supplier:	West Pharma	**Supplier Part Number:**	CETW13
Grade:	N/A	**Drawing reference:**	5003

Sample requirements			
Release:	C/TE/8259 Appendix 2and3 (**See Appendix 3.1.A.1 Facilities and equipment**)	**Full Compendial:**	N/A
Retest:	N/A-Documentation/Label check only	**Retain:**	10, from QC Sample

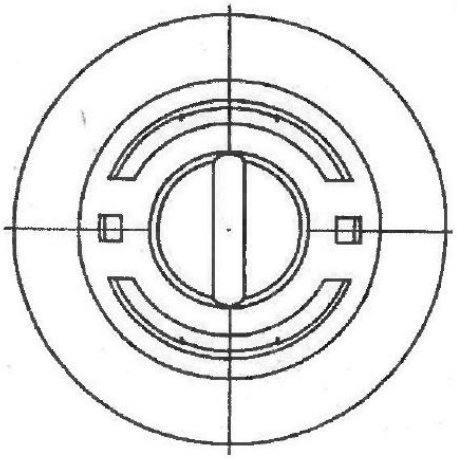
Approval requirement			
Test 1:	Component free from visible contamination, complies with AQL limits	**Test 2:**	Refer to drawing 5003
Test 3:	N/A	**Test 4:**	N/A
Endotoxin Level:	N/A	**Calculation of Bioburden:**	N/A

Documentation requirements			
TSE/BSE Statement:	Yes	**Certificate of Analysis/Conformity:**	Yes
Certificate of Irradiation:	No	**Certificate of Sterility:**	No
Other 1:	N/A	**Other 2:**	N/A

Adelphi Item Code: **CETW13**



–hergestellt aus 0.20 ±0.01 Al.–Band
–produced with 0.20 ±0.01 Al–sheet
–produit avec une bande
Al. 0.20 ±0.01 mm



M 1:1

COPY NOT SUBJECT TO REVISION

THE WEST COMPANY DEUTSCHLAND GMBH

1	Logo	ORZ	5.12.96
Index	Änderung Modification	Name Nom name	Datum Date Date

Ersatz für: Remplace: Replacement for:

Ersetzt durch: Remplacé par: Replaced by:

Maßstab: Ech: Scale: 5:1 | gez: dessiné: drawn: MMH | gepr: contr: checked: 11.12.95 | Name Nom name 4.1.96 | Datum Date Date 28.3.94

Bördelkappe mit Mittelabriß
Aluminium seal with center tear off
Capsule aluminium a opercule central detachable

Art. Nr. / Art. No.: 5003

Primary packaging

The frozen IMP vials were labelled by Albany Molecular Research Inc. (Glasgow) Limited [AMRI] using the approved clinical label for IV cysteamine bitartrate vials, and then were packed into Correx boxes.

The Correx box size of 20 cm (L) x 7 cm (W) x 7 cm (H) was used for packing and 30 vials were packaged into each box. Each IMP box had a dosage sufficient for a 10-day course treatment per patient (3 vials per day). Primary packaging was carried out by Albany Molecular Research Inc. (Glasgow) Limited [AMRI]. The box and insert are white.

The boxes were manufactured by

Sundolitt Ltd,
Suite A2, Stirling Agricultural Centre,
Stirling, FK9 4RN
United Kingdom.

The inserts were manufactured by

Corplex UK,
Madleaze Industrial Estate,
Bristol Road, Gloucester, GL1 5SG
United Kingdom.

The technical information of the Correx boxes is provided below.

CORPLEX

Corplex UK, Madleaze Industrial Estate
Bristol Road, Gloucester GL1 5SG, UK
+44 (0)1452 316500 T
+44 (0)1452 529316 F
www.corplex.com

Corplex UK Technical Information

Introduction

The name Correx® applies to a range of extruded corrugated plastic sheet based on a propylene ethylene copolymer. The natural polymer is chemically inert and is generally recognised by legislative authorities as being non-toxic and safe to use in contact with foodstuffs. The polymer has been safely used in large quantities in all the normal thermoplastic conversion processes. Correx® sheet has been marketed since 1972. This Technical Datasheet has been prepared to provide general technical information relating to Correx® sheet and the standard formats in which the sheet is supplied.

Effect of heat

Correx® can be handled at normal processing temperatures. Small quantities of fumes are evolved at about 220°C due to a partial volatilisation of some stabilisers and/or of lower molecular weight hydrocarbons. These gradually increase until at about 300°C decomposition and oxidative pyrolysis proceeds at an appreciable rate.

Burning behaviour

Typical thermal properties for polypropylene copolymer are as follows:

Softening temperature (BS 2782: 102D, ISO R306)	144°C
Crystalline melting point	165 – 175°C
Flash ignition temperature	ca 350°C
Self-ignition temperature	Ca 380°C
Calorific value	11000 cal. kg
Specific heat	0.46 cal gm °C
Limiting oxygen index (ASTM D2863)	0.174 – 0.180
Burn rate - Correx sheet (FMVSS 302)	5.3 – 8.2cm/min

CORPLEX

Corplex UK, Madleaze Industrial Estate
Bristol Road, Gloucester GL1 5SG, UK
+44 (0)1452 316500 T
+44 (0)1452 529316 F
www.corplex.com

Correx® twinwall polypropylene sheet is produced in four different die profiles which offer a wide variety of possible configurations. The table below shows some standard production profiles which represent the ideal ration between thickness and GSM to provide the best possible combinations of upright rigidity and surface quality.

	3mm Die Flute Spacing 3.2mm	**4mm Die** Flute Spacing 5.6mm	**8mm Die** Flute spacing 6.5mm	**10mm Die** Flute Spacing 10.2mm
g/m²	**Thickness**	**Thickness**	**Thickness**	**Thickness**
300	2.0mm			
350	2.0mm			
400	2.6mm			
450	2.8mm			
550	3.0mm			
600	3.5mm			
650	3.5mm			
700	3.5mm			
1000		5.0mm		
1050	5.0mm			
1200			7.0mm	
1250		5.5mm		
1350			7.5mm	
1450	5.5mm	6.0mm		
1700			8.0mm	
1800			8.0mm	10.0mm
1950				10.0mm
Maximum width without corona treatment	3080mm	1250mm	2530mm	1250mm
Maximum width with corona treatment	3048mm	1220mm	2500mm	1220mm
Minimum width	135mm	400mm	400mm	400mm
Minimum length	500mm	600mm	580mm	600mm
Maximum length	6000mm	6000mm	4500mm	3000mm

LPCB®

www.redbooklive.com

Certificate of Management System Registration

Certificate Number: 227QMS Issue: 13

Corplex Plastics UK Ltd

having complied with the requirements of:

ISO 9001:2015
Quality Management Systems - Requirements

are certified by BRE Global Ltd. and are authorised to use the LPCB Certification Mark on stationery and publications related to the following products and/or services:

Corplex Plastics UK Ltd
Unit 7a – 7b Madleaze Road
Gloucester
GL1 5SG
UK

Scope:
Design and development of plastics packaging and other products using thermoforming, injection moulding and structural foam, and conversion of structural sheet material. Manufacture of structural sheet and conversion into packaging and other products including flame retardant materials.

This certificate is maintained and held in force through regular surveillance activities.

Signed for BRE Global Ltd.	Phil Clare BGM Assessment Services	20 August 2020 Date of this Issue	15 May 2021 Expiry Date	27 January 1997 Date of First Issue

UKAS MANAGEMENT SYSTEMS 0007

bre

80018

The cysteamine bitartrate IMP box with vials and the IMP box with box label are provided in **Figure 1 and 2** below.

Figure 1: *Shows a representative box with IV cysteamine bitartrate vials, 30 IMP vials packed in a box that has a dosage for a course of 10 days treatment per patient.*

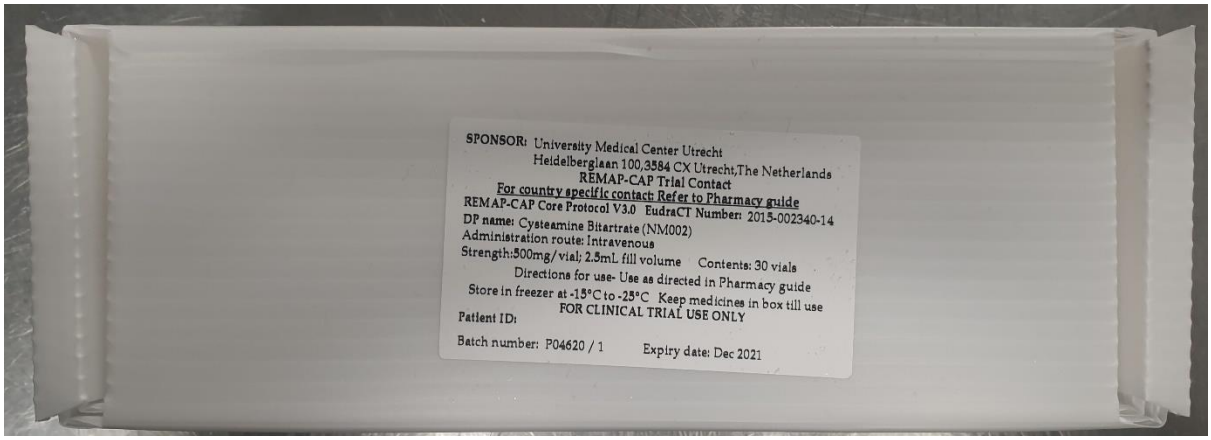


Figure 2: *Shows a representative IMP box with the box label.*

2.1.P.7 Stability

Albany Molecular Research Inc. (Glasgow) Limited [AMRI] carried out stability studies according to the appropriate ICH guidance documents, approved stability protocol and relevant AMRI Glasgow SOPs.

STABILITY OF NON-GMP BATCH

Manufacturing date: 05/2020

The non-GMP batch was manufactured using the same formula as the intended GMP batch, so the stability data generated from the non-GMP batch were considered representative for shelf-life estimation of the clinical batch. Vials of drug product from the non-GMP technical batch (Batch number: 001/NVB/20) were stored under ICH conditions at -20°C and stability testing was completed as shown in **Table** below.

Table: Batch details

Batch Number	Product description	Stability number	Stability start date
001/NVB/20	200 mg/mL cysteamine bitartrate*	RS002/21	19 May 2020

*2.5 mL liquid drug product in each vial.

Storage conditions, stability timepoints and test details are provided in the **Table** below. Initially, NovaBiotics planned stability studies up to 12-month for the non-GMP batch. As the IMP showed good stability at 12-months, long term stability testing was planned up to 24 months.

Storage condition	Initial (T =0)	7 Months	8 Months	9 Months	10 Months	11 Months	12 Months	18 Months	24 Months
-20°C	A	B*	BC	BC	BC	BC	BC	BC	BC

A: Appearance, pH, osmolality, assay, related substances, sub-visible particulates, freeze/thaw

B: Appearance, pH, assay, related substances

C: Sub-visible particulates

Freeze/thaw = 3 cycles, assessing appearance, pH, assay/purity after each cycle

*Only appearance, assay and related substances analysis was performed, pH was not done at 7 months.

The stability data for the non-GMP technical batch 001/NVB/20 are provided in the **Table** below. These data were considered as supportive stability data for estimating the shelf life of the clinical batch.

200 mg/mL cysteamine bitartrate, Lot: 001/NVB/20, Storage condition: -20°C											
Test	**Stability specification**		**Initial (T = 0)**	**7 Months**	**8 Months**	**9 Months**	**10 Months**	**11 Months**	**12 Months**	**18 Months**	**24 Months**
Appearance	Clear, colourless solution free from visible particulates		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	
pH	Report results		5.5	ND	5.7	5.6	5.6	5.6	5.6	5.6	
Osmolality ($mOsmkg^{-1}$)	Report results		234	ND	ND	ND	ND	ND	ND	ND	
Assay (mg/mL)	90.0% -105.0%		102.0	105.9	100.6	101.3	101.1	99.4	100.9	100.9	
Purity	NLT 95%		98.3	97.5	97.8	97.8	98.2	97.8	98.7	98.7	
Impurities (Related substances)	Cystamine (base)	≤5.0%	1.61	2.40	2.16	2.05	1.72	2.13	2.09	2.12	
	Any single unknown impurity	≤0.15%	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	
	Total unknown impurity	≤0.5%	0.14	0.13	0.09	0.11	0.12	0.10	0.09	0.13	
	Total impurities	≤5.0%	1.75	2.53	2.25	2.16	1.84	2.23	2.18	2.25	
Sub-visible particulates	Ph Eur 2.9.19/USP <788> Method 1		PASS	ND	PASS	PASS	PASS	PASS	PASS	PASS	

ND: Not Done.

IMP meets the expectation for appearance and pH based on target drug profile at T = 182 months. There was no significant change observed for appearance and pH for batch 001/NVB/20 after 182 months storage at -20°C.

Sub-visible particulates were measured directly from the sample vial and was carried out as per USP <788> method 1. Result at T = 0 was within the typical specification criteria of the number particles with diameter ≥10 µm per vial ≤6000 = PASS and number particles with diameter ≥25 µm per vial ≤600 = PASS and remained so after 182 months storage at -20°C.

Significant increase in both assay and related substances at T = 7 months when compared to the initial timepoint, T = 0. For the related substances, it was only the cystamine (base) which had significantly increased, relative area for RRT 3.06 and RRT 3.38 were comparable with T = 0. The significant increase in both the assay and the cystamine (base) were monitored at the future later timepoints.

Significant decrease in assay at T = 8 months when compared to T = 7 months however at T = 9 months, the assay was comparable with the previous timepoint (T = 8 months). A new batch of reference material was used for stability technical batch analysis (storage: -20°C) at T = 8 months timepoint. Therefore, on review, it appeared that the response of the previous standard material (storage: 2-8°C) was the root cause of the high assay result at T = 7 months.

During the validation which was carried out in parallel with the T = 8 months and T = 9 months analysis, it was highlighted that the freezing rate of the vials across the technical batch was variable resulting in the variability of the cystamine (base) impurity seen between the timepoints of the stability study. The was investigated and it was confirmed that the cystamine (base) was the only impurity impacted by the variable freezing time of the technical batch vials. This was monitored at the future later timepoints. No significant change in total impurities at T = 8 months and T = 9 months was observed.

No significant change in assay at T = 10 months from the previous timepoint was observed. The assay result obtained at T = 11 months was comparable with theoretical. However, there was a slight decrease compared to T = 0 data with 97.5% recovery. The assay results obtained for vial 1 and vial 2 at T = 11 months were comparable. The recovery v theoretical at the T = 12 months timepoint was within 98.0-102.0%. There was no significant change in assay at the T = 12 months timepoint.

The recovery v theoretical at the T = 18 months timepoint was within 98.0-102.0%. There was no significant change in assay at the T = 18 months timepoint when compared to T = 0. , the recovery v T = 0 was within 98.0-102.0%. There was no significant change in assay throughout the stability study when stored at conditions -20°C.

A significant decrease in cystamine (base) was observed at T = 10 months when compared to T = 9 months. However, this was comparable to the % rel area seen to T = 0. There was a significant increase in cystamine (base), >0.3% rel area, observed at T = 11 months when

compared to T = 10 months. These were due to the variation seen between the freezing rate of the vials when the drug product was set down at -20°C. As the cystamine (base) result was comparable with what has been obtained at previous timepoints, this confirmed that the variation seen in cystamine (base) was not stability related. There was no significant change in any of the other impurities.

There was no significant increase in total or individual impurities at the T = 182 months timepoint when compared to T = 121 months. There was an increase in cystamine (base) of ~0.54% rel area from T = 0 to the final timepoint, T = 182 months. No variability in the cystamine (base) at the T = 182 months timepoint. No significant increase in any other impurity over the course of the 182 months stability study.

STABILITY OF GMP BATCH

GMP batch was manufactured on 22 Dec 2020 and stored at -20°C. As non-GMP stability testing showed good stability for IV cysteamine bitartrate up to 10 months, it was decided to carry out stability testing for the GMP batch at a 6, 9, 12, 18 months and if required at the end of the study. If the trial ends before 18 months, the 18-month stability testing will not be required. Release testing results can be used for initial T = 0 timepoint if samples are placed on stability within 30 calendar days of initiation of release testing. Any testing outside the 30 days will be re-tested.

Release testing and Sstability studies of the GMP batch wereas carried out by Curia (Scotland) in line with current ICH requirements relevant AMRI to Curia (Scotland) Glasgow SOPs and approved stability protocol.

Table: Batch details

Batch Number	Product description	Stability study protocol	Stability start date
P04620	200 mg/mL cysteamine bitartrate	S00221	209 Apr 2021

Samples were stored within AMRI Curia (Scotland)Glasgow stability cabinets in the original containers, as received. Product vials for Stability testing vials were held in an upright position. Regulatory reference sample vials were held upright at the defined product storage condition. Contingency vials were stored upright. The stability cabinets were monitored continuously throughout this study for any excursions in storage conditions relevant to the product.

Storage conditions, stability timepoints and test details are provided in the **Table** below.

Storage condition	Initial (T = 0)	6 Months	9 Months	12 Months	End of Trial Months
-20°C	A*	B	BC	BC	BC

A: Appearance, pH, osmolality, assay, related substances, ID, volume in container, sub-visible particulates, endotoxin and sterility.
B: Appearance, pH, assay, related substances
C: Sub-visible particulates, endotoxin, sterility

*IMP batch release testing results were used for T = 0 stability results. The testing breached the set-down window period of 30 days by few days as the reference sample was found to be degraded upon use in testing, the cause of which was not determined. However, a fresh reference sample was obtained which showed expected results in the first attempt. Considering there was only a small delay from the 30 days window period, it was decided not necessary to perform another T = 0 assessment.

The stability data for the GMP technical batch P04620 are provided in the **Table** below.

200 mg/mL cysteamine bitartrate, Lot: P04620, Storage condition: -20°C							
Test	**Stability specification**		**Initial (T -0)**	**6 Months**	**9 Months**	**12 Months**	**End of Trial**
Appearance	Clear, colourless solution free from visible particulates		Complies	Complies			
pH	Report results		5.5	5.5			
Osmolality (mOsm/kg)	Report results		219	ND			
Volume in Container (Extractable Volume)	NLT 2.2 mL		2.4 mL	ND			
Identification (Retention Time)	Retention peak compares to the reference standard		Complies	Complies			
Assay (mg/mL)	95.0% -105.0%		100.8%	101.4%			
Purity	NLT 95%		95.9%	95.6%			
Impurities (Related substances)	Cystamine (base)	≤5.0%	3.90	4.05			
	Any single unknown impurity	≤0.15%	Complies	Complies			
	Total unknown impurity	≤0.5%	0.24	0.34			
	Total impurities	≤5.0%	4.14	4.39			
Identification (DAD Spectra)	λ max in the reference solution and in the sample solution are the same within ±3 nm		PASS	ND			
Particulate Matter	Complies with Ph.Eur./USP <788> Method I		PASS	PASS			
Endotoxins	NMT 10 EU/mL		PASS	PASS			
Sterility	Sterile		PASS	PASS			

ND: Not Done; Sterility testing was subcontracted to Charles River Laboratories Ireland Ltd, Ballin.

Out Of Specifications (OOS)

At 6 months stability testing of the GMP batch, out-of-specifications (OOS) was found for cysteamine (base) impurity. Specification for impurity was set at NMT 5.0% but the initial results showed 5.77%. An investigation was carried out by Curia (Scotland), and it was found that the high impurity results were due to the samples being in stored in the amber glassware before the testing which therefore have caused increased cysteamine (base) impurity level. During validation it was noted that the cysteamine (base) impurity increased significantly over time when the product was stored in amber glassware. Therefore, the results cannot attribute to product degradation at 6-month stability study and the initial result was invalidated. Repeat testing from the fresh sample vials showed cysteamine (base) impurity was within the specification criteria, and the results showed no impact on the stability data and on trend with previous analysis.

Furthermore, at 6 months stability test, the bacterial endotoxin testing stability results showed an OOS for endotoxin in just one well. All samples were tested in duplicate, one well indicated no endotoxin whereas the other duplicate well indicated an endotoxin level of 28.1EU/mL against an endotoxin limit of 10EU/mL. This OOS result was investigated. Root cause of the initial OOS result obtained was believed to be due to spontaneous (environmental) contamination (samples are tested on kinetic tube reader on lab bench which could be susceptible to contamination) of one well. The initial result was invalidated. Repeat testing from the original (vial 1) showed results of <2EU/mL and the GMP product met the stability criteria at 6 months stability testing.

Shelf-Life extension plan

The stability data collected thus far for the cysteamine bitartrate IV product confirm that the IMP is stable for 18 months when stored frozen at -15 to -25°C, starting from the manufacturing date of the product. The stability data obtained from the non-GMP batch allowed to define an estimated shelf-life of **18 months** for the product.

NovaBiotics has planned ongoing stabilities studies both for the non-GMP (up to 24 months) and GMP batches (up to 18 months) that would allow to extend the shelf-life for the product. The shelf-life extensions in the future will be based on the available real time stability data for the product that meets the predetermined specifications and acceptable criteria. At present, there is no plan to extrapolate the stability data to estimate the shelf-life extension. However, if required, NovaBiotics will analyse the trends in the stability data and will estimate the shelf-life based on the extrapolation criteria outlined in the following guidelines:

- MHRA, Points to consider when preparing the IMP dossier
- Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017)

Storage condition and stability results

The drug product must be stored frozen at -15 to -25°C. For the clinical batch, updated stability tables will be provided (if requested by the relevant authority) and any unexpected results or out of specification be revelated over the stability testing period that will potentially impact on quality, efficacy, and safety of drug product will be communicated immediately to the relevant authority, and a further decision plan will be undertaken. Furthermore, any unexpected results which may invalidate the extrapolated shelf life (if extrapolation used to extend the shelf-life) will be communicated to the relevant regulatory authorities, and the clinical batches will be recalled.

IN-USE STABILITY OF DRUG PRODUCT IN CLINIC USE

In-use study to assess stability of drug product vials in clinic was carried out at 2-8°C for 7 days and at ambient temperate for 48 hours.

Materials, reagents, and equipment

All materials and reagents were of appropriate grade/quality for intended use. All equipment was suitably calibrated.

Materials and reagents

Materials and reagents	Details
Cysteamine bitartrate drug product	001/NVB/20
Water	In-house supply
Acetonitrile	Lot: 20J061957
99.9% Methanol	Lot: 2066189
85% Phosphoric Acid	Lot: BCBZ515
Sodium Dodecyl Sulphate	Lot: MKCL7761

Results

Appearance and pH, 2-8°C study

Time-point/storage	Appearance	pH
T = 0 (Initial)	Clear, colourless solution with no visible particulates	5.8
T = 1 day	Clear, colourless solution with no visible particulates	5.7
T = 2 days	Clear, colourless solution with no visible particulates	5.5
T = 3 days	Clear, colourless solution with no visible particulates	5.5
T = 4 days	Clear, colourless solution with no visible particulates	5.6
T = 5 days	Clear, colourless solution with no visible particulates	5.6
T = 6days	Clear, colourless solution with no visible particulates	N/A
T = 7 days	Clear, colourless solution with no visible particulates	5.7

Note: *pH analysis for T = 6 days (2-8°C study) was not performed in error. As this was not the final time point, the study was not repeated in order to obtain a pH result for the T = 6 days.*

Appearance and pH, ambient study

Time-point/storage	Appearance	pH
T = 0 (Initial)	Clear, colourless solution with no visible particulates	5.6
T = 3 hours	Clear, colourless solution with no visible particulates	5.6
T = 6 hours	Clear, colourless solution with no visible particulates	5.6
T = 10 hours	Clear, colourless solution with no visible particulates	5.6
T = 24 hours	Clear, colourless solution with no visible particulates	5.7
T = 34 hours	Clear, colourless solution with no visible particulates	5.6
T = 48 hours	Clear, colourless solution with no visible particulates	5.6

No significant change in appearance or pH was observed over the course of the 2-8°C and ambident studies.

Sub-visible particles

Sub-visible particles (µm), 2-8°C study

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
T = 0 (Initial)	42	0	PASS
T = 3 days	21	4	PASS
T = 7 days	17	0	PASS

**Number particles with diameter ≥10µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.*

Sub-visible particles (µm), ambient study

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
T = 0 (Initial)	0	0	PASS
T = 10 hours	42	25	PASS
T = 48 hours	4	0	PASS

Number particles with diameter ≥10µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.* ***Note:* *Sub-visible particulate analysis for T = 24 hours was not performed in error. Due to the sub-visible particulate testing being carried out at the time points immediately before and after T = 24 hours, the study was not repeated for T = 24 hours.*

No significant change in sub-visible particulates was observed over the course of the 2-8°C and ambident studies.

Assay and Related Substances

Assay, 2-8°C study

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0 (Initial)	201.269	201.257	201.263	100.6	-
T = 1 day	202.208	201.210	201.709	100.9	100.2
T = 2 days	198.624	198.540	198.582	99.3	98.7
T = 3 days	199.156	199.009	199.082	99.5	98.9
T = 4 days	-	-	-	-	-
T = 5 days	-	-	-	-	-
T = 6days	200.391	201.629	201.010	100.5	99.9
T = 7 days	197.289	197.940	197.614	98.8	98.2

[1]As percentage of theoretical 200 mg/mL; [2]As percentage of initial (T = 0) result. ***Note:*** *No assay or related substances data for the T = 4 and T = 5 days timepoints was obtained due to chromatographic issues. As data was obtained prior to and following these timepoints the analysis was not required to be repeated.*

No assay or related substances data for the T = 4 and T = 5 days timepoints was obtained due to chromatographic issues. As data was obtained prior to and following these timepoints the analysis was not required to be repeated.

At present, no reason to establish a root cause for the atypical chromatography has been achieved. All materials and reagents were compared across all studies for this product and there is no difference between column, materials or specifics used when the issue has been observed. This was investigated and this issue will be further highlighted if obtained in future analysis for this product [**See Section 2.1.P.5.3 Investigations (page =148)**].

Assay, ambient study

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0 (Initial)	202.100	203.118	202.609	101.3	-
T = 3 hours	202.341	202.098	202.220	101.1	99.8
T = 6 hours	202.634	201.851	202.242	101.1	99.8
T = 10 hours	200.234	201.183	202.242	100.4	99.1
T = 24 hours	201.209	205.321	203.265	101.6	100.3
T = 34 hours	206.257	207.707	206.982	103.5	102.2
T = 48 hours	204.158	203.886	204.022	102.0	100.7

[1]As percentage of theoretical 200 mg/mL; [2]As percentage of initial (T = 0) result.

No significant change in assay over the course of the 2-8°C or ambident study was observed. All recoveries v T = 0 were within the typical criteria of 98.0 -102.0% except for T = 34 hours. However, the recovery drops to within this criterion at the T = 48 hours which shows the slight increase at T = 24 hours is anomalous and potentially due to a preparation error.

Related Substances, 2-8°C study

RRT	Time-point/storage and amount (% Area)							
	Initial (T = 0)	**T = 1 day**	**T = 2 days**	**T = 3 days**	**T = 4 days**	**T = 5 days**	**T = 6 days**	**T = 7 days**
0.72	<LOQ	0.05	<LOQ	<LOQ	-	-	<LOQ	<LOQ
0.73	0.05	0.05	<LOQ	<LOQ	-	-	<LOQ	<LOQ
0.84	ND	ND	<LOQ	<LOQ	-	-	<LOQ	<LOQ
1.18	<LOQ	<LOQ	<LOQ	<LOQ	-	-	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ	<LOQ	-	-	<LOQ	<LOQ
1.57	<LOQ	<LOQ	<LOQ	<LOQ	-	-	<LOQ	<LOQ
3.49	0.12	0.11	0.11	0.10	-	-	0.08	0.06
3.71	<LOQ	<LOQ	<LOQ	<LOQ	-	-	<LOQ	ND
Cystamine (base)	2.45	2.42	2.85	2.99	-	-	4.11	4.55
Total*	**2.62**	**2.63**	**2.96**	**3.09**	-	-	**4.19**	**4.61**

**Sum of related substances ≥0.05%, totals take from chromatographic software.*

No significant increase in individual or total impurities after T = 1 day at 2-8°C storage was observed. At T = 2 days, there is an increase of ~0.4% relative area in the cystamine (base) and this continues to increase at each of the remaining timepoints.

The average impurities of the two vials analysed at each timepoint is reported. As seen in previous studies, there has been some variation in the cystamine (base) content between vials observed due to the variable freezing rate of the drug product when stored at -20°C [**See Section 2.1.P.5.3 Investigations (Page = 148)**]. The cystamine (base) between both vials for the 2-8°C study was comparable.

There was no significant change in any of the other related substances over the course of the study.

Related Substances, ambient study

RRT	Time-point/storage and amount (% Area)						
	Initial (T = 0)	**T = 3 hours**	**T = 6 hours**	**T = 10 hours**	**T = 24 hours**	**T = 34 hours**	**T = 48 hours**
0.84	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
1.18	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
1.57	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
3.49	0.11	0.10	0.10	0.10	0.08	0.09	0.08
3.71	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	2.05	2.10	2.17	2.24	2.48	2.63	2.95
Total*	2.16	2.20	2.27	2.34	2.56	2.72	3.03

**Sum of related substances ≥0.05%, totals take from chromatographic software.*

No significant increase in individual or total impurities after T = 3 hours and T = 6 hours was observed. At T = 10 hours, there was an increase in cystamine (base) >0.1% relative area from the T = 6 hours timepoint. From the T = 10 hours timepoint, there was an increase in cystamine (base) of ~0.2-0.3% relative area at each of the remaining timepoints.

Once again for the ambient study, the average impurities of the two vials analysed at each time point was reported. As seen in previous studies, there had been some variation in the cystamine (base) content between vials observed due to the variable freezing rate of the drug product when stored at -20°C [**See Section 2.1.P.5.3 Investigations (Page = 148)**]. During the ambient study, there was variability observed between the two vials and the % relative area of cystamine (base) was consistently higher in vial 1 when compared to vial 2. At each of the time points, vial 1 consistently had a % relative area of ~0.4-0.5% greater than vial 2.

There was no significant change in any of the other related substances over the course of the study.

Conclusion

No significant change in appearance, pH and sub-visible particulates was observed over the course of the 2-8°C and ambident studies. No significant increase in individual or total impurities on T = 1 day at 2-8°C storage and up to T = 6 hours in ambient storage. The % relative area in the cystamine (base) increased after day 1 and after 6 hours at 2-8°C and ambident studies respectively.

IN-USE STUDY TO ASSESS STABILITY OF CYSTEAMINE BITARTRATE DRUG PRODUCT IN CLINIC: EXTENDED STUDY

As the 7 days In-use stability study in clinic showed that the IMP cysteamine bitartrate was stable up to 7 stays when stored refrigerated at 2-8°C, NovaBiotics extended the study and

assessed the In-use stability of cysteamine bitartrate in clinic up to and including T = 10 days at 2-8°C storage condition. In the extended study, stability of cysteamine bitartrate was assessed only at time points, T = 0 (initial) and T = 8, 9 and 10 days.

Materials, reagents, and equipment

All materials and reagents were of appropriate grade/quality for intended use. All equipment was suitably calibrated.

Materials and reagents

Materials and reagents	Details
Cysteamine bitartrate drug product	001/NVB/20
Water	In-house supply
Acetonitrile	Lot: 20L152008
99.9% Methanol	Lot: 2169132
85% Phosphoric Acid	Lot: BCBZ515
Sodium Dodecyl Sulphate	Lot: MKCL7761

Results

Appearance and pH, 2-8°C study

Time-point/storage	Appearance	pH
T = 0 (Initial)	Clear, colourless solution with no visible particulates	5.6
T = 8 days	Clear, colourless solution with no visible particulates	5.6
T = 9 days	Clear, colourless solution with no visible particulates	5.6
T = 10 days	Clear, colourless solution with no visible particulates	5.6

No significant change in appearance or pH was observed over the course of the 10-day study.

Sub-visible particles

Sub-visible particles (µm), 2-8°C study

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
T = 0 (Initial)	0	0	PASS
T = 8 days	8	4	PASS
T = 9 days	4	0	PASS
T = 10 days	8	4	PASS

**Number particles with diameter ≥10 µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.*

No significant change in sub-visible particulates was observed over the course of the 2-8°C study.

Assay and Related Substances

Assay, 2-8°C study

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0 (Initial)	200.102	201.233	200.668	100.3	-
T = 8 days	200.922	200.456	200.689	100.3	100.0
T = 9 days	201.284	199.298	200.291	100.1	99.8
T = 10 days	202.080	202.023	202.051	101.0	100.7

[1]As percentage of theoretical 200 mg/mL; [2]As percentage of initial (T = 0) result.

No significant change in assay over the course of the 2-8°C study was observed. All recoveries v T = 0 were within the typical criteria of 98.0 -102.0% and all recoveries v theoretical were within the typical criteria of 98.0 -102.0%.

Related Substances, 2-8°C study

RRT	Time-point/storage and amount (% Area)			
	Initial (T = 0)	T = 8 days	T = 9 days	T = 10 days
0.84	<LOQ	<LOQ	<LOQ	<LOQ
1.18	<LOQ	<LOQ	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ	<LOQ
1.57	<LOQ	<LOQ	<LOQ	<LOQ
3.49	0.11	0.08	0.08	0.07
3.71	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	2.22	3.15	3.37	3.56
Total*	**2.33**	**3.23**	**3.45**	**3.63**

**Sum of related substances ≥0.05%, totals take from chromatographic software.*

At T = 8 days, there was a significant increase in the cystamine (base) of ~0.9% relative area from the T = 0 timepoint, this impurity continued to increase by approximately 0.2% relative area at each of the remaining timepoints.

The average impurities of the two vials analysed at each time point was reported. As seen in previous studies, there had been some variation in the cystamine (base) content between vials observed due to the variable freezing rate of the drug product when stored at -20°C [**See Section 2.1.P.5.3 Investigations (Page = 148)**]. During the extended 2-8°C In-use study, there was variability observed between the two vials and the % relative area of cystamine (base) was consistently higher in vial 1 when compared to vial 2. At each of the time points, vial 1 consistently had a % relative area of ~0.4-0.5% greater than vial 2.
There was no significant change in any of the other related substances over the course of the study.

ASSESSMENT OF INFUSION FLUID STABILITY AND COMPATIBILITY WITH IV ADMINISTRATION SETS

Cysteamine bitartrate 200 mg/mL is a concentrated solution and needs to be diluted prior to administration intravenously. The diluted cysteamine bitartrate drug product will be given by infusion. To verify that the diluted cysteamine bitartrate solution is stable during infusion and compatible with IV sets routinely used in the hospitals, the following tests were carried out by AMRI as described below.

- In-use study to assess the stability of the diluted cysteamine bitartrate drug product in the infusion bags.
- Compatibility of diluted cysteamine bitartrate solution with the IV administration set.

In-use stability of cysteamine bitartrate drug product in infusion bags

The liquid product of the cysteamine bitartrate IMP was assessed at two concentrations, 1.75 mg/mL in 100 mL 0.9% sodium chloride solution and 10 mg/mL in 50 mL 0.9% sodium chloride solution and assessed for stability over 24 hours at both 2-8°C and ambient conditions. The lower concentrations, as worst-case scenario was also assessed for compatibility with IV administration sets.

Materials, reagents, and test method

The following materials and reagents, and test method were used for the analysis.

Materials and reagents

Materials and reagents	Details
Cysteamine bitartrate drug product	001/NVB/20
Water	In-house supply
0.9% w/v sodium chloride 100 mL	Lot: FE1307G
0.9% w/v sodium chloride 50 mL	Lot: FE1306G
5 mL syringe	Lot: 20190508
1 mL syringe	Lot: 20190705
21G needle 40mm x 0.8mm	Lot: 200515

Test method

Test	Method/SOP
Appearance	C.TE.8257.06
Assay and related substances by HPLC	ADP369
Sub-visible particulates	C.EQ.8042.10

Preparation of 1.75 mg/mL cysteamine bitartrate in 100 mL 0.9% w/v sodium chloride infusion solution

- Transferred 0.8 mL of 200 mg/mL cysteamine bitartrate drug product into the 100 mL infusion bag using a needle and 1 mL syringe.
- Inverted the infusion bag 10 times to ensure homogenous solution.
- Repeated the above steps to prepare two bags in total.

Preparation of 10 mg/mL cysteamine bitartrate in 50 mL 0.9% w/v sodium chloride infusion solution

- Transferred 2.5 mL (contents of 1 vial) of 200 mg/mL cysteamine bitartrate drug product into the 50 mL infusion bag using a needle and 5 mL syringe.
- Inverted the infusion bag 10 times to ensure homogenous solution.
- Repeated the above steps to prepare two bags in total.

Sample storage

One infusion bag at each concentration was stored at ambient conditions; the remaining bag at each concentration was stored at 2-8°C. Samples were removed after 0, 3, 6 and 24 hours. Additionally, a sample was also removed from a 0.9% w/v sodium chloride infusion bag containing no cysteamine bitartrate and tested as a control.

Analysis and acceptance criteria

At each time point, 5 mL of sample solution was removed from each bag using a needle and syringe. 3 mL of the sample solution was transferred to a glass sample vial for sub-visible particulate testing and 2 mL was transferred to a glass sample vial for appearance and assay/related substances. Analytical testing was carried out according to **Table** below.

Testing matrix

Test	Sample			
	T = 0 (bag)	T = 3 hour	T = 6 hour	T = 24 hour
Appearance	√	√	√	√
Sub-visible particles*	√	√	√	√
Assay and related substances	√	√	√	√

**Sub visible particulate testing was carried out on reduced volumes as appropriate for development study (1 mL tare + 4 x 0.5 mL sample runs)*

Results

Appearance, 1.75 mg/mL at both 2-8°C and Ambient

Time-point/storage	Appearance
T = 0	Clear, colourless solution with no visible particulates
T = 3 h	Clear, colourless solution with no visible particulates
T = 6 h	Clear, colourless solution with no visible particulates
T = 24 h	Clear, colourless solution with no visible particulates

Appearance, 10 mg/mL at both 2-8°C and Ambient

Time-point/storage	Appearance
T = 0	Clear, colourless solution with no visible particulates
T = 3 h	Clear, colourless solution with no visible particulates
T = 6 h	Clear, colourless solution with no visible particulates
T = 24 h	Clear, colourless solution with no visible particulates

Sub-visible particulates

Sub-visible particulates (µm), 1.75 mg/mL at 2-8°C

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
Initial (T = 0)	5	0	PASS
T = 24 h	28	23	PASS

**Number particles with diameter ≥10 µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.*

Sub-visible particulates (µm), 1.75 mg/mL at Ambient

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
Initial (T = 0)	2	0	PASS
T = 24 h	18	10	PASS

**Number particles with diameter ≥10 µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.*

Sub-visible particulates (µm), 10 mg/mL at 2-8°C

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
Initial (T = 0)	7	3	PASS
T = 24 h	12	0	PASS

**Number particles with diameter ≥10 µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.*

Sub-visible particulates (µm), 10 mg/mL at Ambient

Time-point/storage	Count/vial*		Pass/Fail*
	≥10 µm	≥25 µm	
Initial (T = 0)	17	10	PASS
T = 24 h	25	7	PASS

**Number particles with diameter ≥ 10 µm per vial <6000 = PASS and number particles with diameter ≥25 µm per vial <600 = PASS.*

Assay and Related Substances

Assay, 1.75 mg/mL at 2-8°C

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0	1.466	-	-	91.6	-
T = 3 h	1.468	1.468	1.468	91.8	100.2
T = 6 h	1.475	1.475	1.475	92.2	100.6
T = 24 h	1.481	1.478	1.480	92.5	101.0

[1]As percentage of theoretical 1.75 mg/mL; [2]As percentage of initial (T = 0) result.

Assay, 1.75 mg/mL at Ambient

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0	1.496	-	-	93.5	-
T = 3 h	1.496	1.498	1.497	93.5	100.0
T = 6 h	1.493	1.493	1.493	93.3	99.8
T = 24 h	1.510	1.506	1.508	94.3	100.8

[1]As percentage of theoretical 1.75 mg/mL; [2]As percentage of initial (T = 0) result.

Assay, 10 mg/mL at 2-8°C

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0	8.100	-	-	81.0	-
T = 3 h	8.154	8.061	8.108	81.5	100.1
T = 6 h	8.211	8.257	8.234	82.1	101.7
T = 24 h	8.170	8.207	8.188	81.7	101.1

[1]As percentage of theoretical 10 mg/mL; [2]As percentage of initial (T = 0) result.

Assay, 10 mg/mL at Ambient

Time-point/ storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = 0	7.853	-	-	78.5	-
T = 3 h	7.855	7.869	7.862	78.5	100.1
T = 6 h	7.986	7.901	7.944	79.9	101.1
T = 24 h	7.933	7.980	7.956	79.3	101.3

[1]As percentage of theoretical 10 mg/mL; [2]As percentage of initial (T = 0) result.

Related substances, 1.75 mg/mL at 2-8°C

RRT	Time-point/storage and amount (% Area)			
	Initial (T = 0)	T = 3 hrs	T = 6 hrs	T = 24 hrs
1.11	0.10	0.10	0.10	0.10
1.17	<LOQ	<LOQ	<LOQ	<LOQ
1.24	<LOQ	<LOQ	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ	<LOQ
1.57	<LOQ	<LOQ	<LOQ	<LOQ
3.49	0.13	0.13	0.14	0.14
3.71	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	1.75	1.69	1.75	1.69
Total*	**1.98**	**1.92**	**1.99**	**1.93**

*Sum of related substance ≥0.05%, totals taken from chromatographic software.

Related substances, 1.75 mg/mL at Ambient

RRT	Time-point/storage and amount (% Area)			
	Initial (T = 0)	T = 3 hrs	T = 6 hrs	T = 24 hrs
1.11	0.10	0.10	0.10	0.11
1.17	<LOQ	<LOQ	<LOQ	<LOQ
1.24	<LOQ	<LOQ	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ	<LOQ
1.57	<LOQ	<LOQ	<LOQ	<LOQ
3.49	0.13	0.14	0.14	0.14
3.71	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	1.72	1.75	1.80	1.73
Total*	**1.95**	**1.99**	**2.04**	**1.98**

*Sum of related substance ≥0.05%, totals taken from chromatographic software.

Related substances, 10 mg/mL at 2-8°C

RRT	Time-point/storage and amount (% Area)			
	Initial (T = 0)	**T = 3 hrs**	**T = 6 hrs**	**T = 24 hrs**
1.11	0.10	0.05	0.05	0.05
1.17	<LOQ	<LOQ	<LOQ	<LOQ
1.24	<LOQ	<LOQ	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ	<LOQ
2.81	0.10	ND	ND	ND
3.49	0.13	0.13	0.13	0.13
3.71	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	1.92	1.86	2.08	2.05
Total*	**2.24**	**2.04**	**2.26**	**2.23**

*Sum of related substance ≥0.05%, totals taken from chromatographic software.

Related substances, 10 mg/mL at Ambient

RRT	Time-point/storage and amount (% Area)			
	Initial (T = 0)	**T = 3 hrs**	**T = 6 hrs**	**T = 24 hrs**
1.11	0.05	<LOQ	0.06	<LOQ
1.17	<LOQ	<LOQ	<LOQ	<LOQ
1.24	ND	ND	ND	ND
1.32	<LOQ	<LOQ	<LOQ	<LOQ
2.81	ND	ND	ND	ND
3.49	0.13	0.13	0.13	0.13
3.71	<LOQ	<LOQ	<LOQ	<LOQ
Cystamine (base)	2.21	2.28	2.49	2.52
Total*	**2.38**	**2.41**	**2.68**	**2.65**

*Sum of related substance ≥0.05%, totals taken from chromatographic software.

Conclusion

There is no change in appearance and sub-visible particulates over the stability period for concentrations, 1.75 mg/mL and 10 mg/mL at either storage condition.

There is no significant change in assay or related substances over the course of the 24 h stability study for the 1.75 mg/mL bags at either storage condition. All assay recoveries v T = 0 throughout the study were within 98.0 – 102.0% and there was no significant increase in individual or total impurities.

There is no significant change in assay over the course of the 24 h stability study for the 10 mg/mL bags at either storage condition. All assay recoveries v T = 0 throughout the study were within 98.0 – 102.0%. Variability in cystamine (base) was observed for the 10 mg/mL bags between vials **[See Section 2.1.P.5.3 Investigations (Page = 148)]** and between the timepoints over the 24 h stability study. An increase of 0.3% was observed from T=0 to the T = 24 h timepoint for the cystamine (base) impurity at the ambient storage condition. No

significant change was observed in this impurity when stored at 2-8°C. There was no significant increase in any other individual impurities or total impurities over the course of the stability study at either storage condition.

Note: The volume of a 50 mL infusion bag was measured and shown to be 60 mL and the volume of a 100 mL infusion bag measured and shown to be 110 mL. There was 10 mL over the stated volume for both of the bags. Due to the bag overage, the target concentrations would not have been achieved hence the lower than the anticipated assay results.

Compatibility of cysteamine bitartrate solution with IV administration sets

Preparation of 1.75 mg/mL cysteamine bitartrate in 0.9% w/v sodium chloride infusion solution

- Transferred 0.8 mL of 200 mg/mL cysteamine bitartrate drug product into the 100 mL infusion bag using a needle and 1 mL syringe.
- Inverted the infusion bag 10 times to ensure homogenous solution.
- Repeat the above steps to prepare two bags in total.

Administration

Fresh infusion bags were prepared following the steps above. The bags were attached to the administration sets and the dilute cysteamine bitartrate solution was run from the bag through the set by gravity. The flow rate adjusted to run/administer the entire bag within 15 minutes at ambient temperature. A 10 mL sample was removed at the beginning, middle and end of the administration and the remaining solution stored as a bulk.

Analysis and acceptance criteria

The beginning, middle and end samples were analysed for appearance, assay and related substances as given in the **Table** below.

Testing matrix

Test	Sample		
	Beginning (10 mL)	Middle (10 mL)	End (10 mL)
Appearance	√	√	√
Assay and related substances	√	√	√

Results

Appearance, IV administration sets, 1.75 mg/mL

Time-point/storage	Appearance
T = Beginning	Clear, colourless solution with no visible particulates
T = Middle	Clear, colourless solution with no visible particulates
T = End	Clear, colourless solution with no visible particulates

Assay, IV administration sets, 1.75 mg/mL

Time-point/storage	Preparation 1 [cysteamine bitartrate] (mg/mL)	Preparation 2 [cysteamine bitartrate] (mg/mL)	Mean [cysteamine bitartrate] (mg/mL)	% Recovery vs theoretical[1]	% Recovery vs T = 0[2]
T = Beginning	1.497	1.460	1.479	85.5	-
T = Middle	1.495	1.464	1.480	84.6	100.1
T = End	1.496	1.461	1.479	84.5	99.9

[1]As percentage of theoretical 1.75 mg/mL; [2]As percentage of initial (T = Beginning) result.

Related substances, IV administration sets, 1.75 mg/mL

RRT	Time-point/storage and amount (% Area)		
	T = Beginning	T = Middle	T = End
1.11	0.10	0.10	0.11
1.17	<LOQ	<LOQ	<LOQ
1.32	<LOQ	<LOQ	<LOQ
3.49	0.13	0.13	0.14
3.71	<LOQ	<LOQ	<LOQ
Cystamine (base)	1.74	1.74	1.74
Total*	**1.97**	**1.97**	**1.99**

*Sum of related substance ≥0.05%, totals taken from chromatographic software.

Conclusion

There is a no change in appearance between the beginning, middle and end of the 1.75 mg/mL bags which were administered with the IV administration sets over a period of 15 minutes.

There is no significant change in assay or related substances between the beginning, middle or end of the 1.75 mg/mL bags which were administered with the IV administration sets over a period of 15 minutes.

3. Appendices

3.1.A.1 Facilities and equipment

The manufacturing authorisation certification of Albany Molecular Research Inc. (Glasgow) Limited [AMRI] is provided below. AMRI changed its name to Curia (Scotland) limited in Jul 2021.

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 Version: 23

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 1A

1. **Authorisation Number**

MIA(IMP) Number: MIA(IMP) 19124

2. **Name of Authorisation Holder**

ALBANY MOLECULAR RESEARCH (GLASGOW) LIMITED

3. **Trading Style**

4. **Address(es) of manufacturing/importing site(s)**
(All authorised sites should be listed if not covered by separate licences)

MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
92248	ALBANY MOLECULAR RESEARCH INC. (GLASGOW) LIMITED	BLOCK K, TODD CAMPUS, WEST OF SCOTLAND SCIENCE PARK, ACRE ROAD, GLASGOW, G20 0XA, UNITED KINGDOM

5. **Legally registered address of Authorisation Holder**

TODD CAMPUS, WEST OF SCOTLAND SCIENCE PARK, GLASGOW, G20 0XA, UNITED KINGDOM

6. **Scope of authorisation and dosage forms**

See Annex 2

7. **Legal basis of authorisation**

See Section 1B of authorisation.

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 Version: 23

8. **Name of responsible officer of the competent authority of the member state granting the manufacturing authorisation**

Olumuyiwa Abimbola

SECTION 1A (continued)

9. **Date** 07/05/2020

10. **Annexes attached**

Annex 2

Optional Annexes

Annex 4 (Contract Laboratories)

Annex 5 (Name of Qualified Person)

Annex 6 (Name of Responsible Person)

Annex 8 (Manufactured/Imported products)

Annex 9 (Storage Sites)

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 Version: 23

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 1B

1. This authorisation is granted in accordance with the provisions of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] which implement Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001.

2. It permits the authorisation holder named on page 1 of Section 1 of the authorisation to manufacture, assemble and/or import investigational medicinal products for human use in accordance with Regulation 41 of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] (as detailed in section 3 of this authorisation) and is subject to the provisions identified on page 2 of Section 1 of this authorisation.

3. In this document a Manufacturers Authorisation for Investigational Medicinal Products may be referred to as MIA(IMP) and the Medicines and Healthcare products Regulatory Agency (acting on behalf of the Licensing Authority as defined in Regulation 6 of The Human Medicines Regulations 2012 (SI 2012/1916) may be referred to as MHRA.

4. The authorisation holder must inform the MHRA, in advance, of any change to the details submitted by him and/or included in this authorisation. All changes must be approved by the MHRA to have effect. If the business should change hands, the company or person taking over the business will have to obtain a new authorisation before commencing the manufacture, assembly or importation of investigational medicinal products.

Attention is drawn to the structure of this authorisation (as detailed on page 4 of Section 1) and to its completeness in accordance with that structure. This is of particular relevance where the holder of the authorisation is using it as evidence to a third party in support of claims to carry out those operations and activities to which this authorisation applies on premises and using personnel covered by this authorisation.

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 Version: 23

SECTION 1B (continued)

5. Authorisation Structure

This authorisation is divided into three sections.

(a) Section 1 (this section) identifies the authorisation holder and the responsible officer for the issue of the authorisation. This section would not usually be replaced during routine variations of the authorisation unless the authorisation holder details are varied.

(b) Section 2 lists variations to the authorisation. A replacement section 2 will be issued each time the authorisation is varied.

(c) Section 3 contains the details relating to each site named on the authorisation. Where there is more than one site there will be more than one part to Section 3. When a variation is made to the details of a site named in Section 3 the relevant part of Section 3 will be replaced.

(d) The authorisation holder is required to attach to his authorisation any replacement pages issued by MHRA and to mark or destroy superseded pages as to render them invalid.

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6. Provisions

a) The provisions of Schedule 7 of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] shall apply to the authorisation. For manufacture and/or assembly Parts 1 and 2 of Schedule 7 apply and for importation Parts 1 and 3 of Schedule 7 apply in accordance with Regulation 40(4) of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] subject to Regulation 38(2).

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 Version: 23

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 2

VARIATION HISTORY

This page will be amended if the licence is varied.

Date	Variation Detail
16/03/2004	Initial application
04/05/2004	
03/01/2006	Remove Mr Roger Jones as Production Manager from the Todd Campus site and George Street site. Replace with Mrs Fiona Johnstone as Production Manager
10/03/2006	Change company name from ProPharma to Evotec (Scotland) Ltd. Remove Site 204 George Street, Glasgow G1 1XW. Add Human or animal extracted substances -(Classes of products) Add non-sterile freeze-dried powder. Add Herbal products - (Classes of Products)
13/03/2006	Change address of Licence Holder from 204 George street, Glasgow to Todd Campus, West of Scotland Science Park, Acre Road, Glasgow G20 OXA.
03/12/2007	Variation to replace PM with Dr I MacGilp and QC with Mr P Fullerton and to add Contract Laboratory Sites.
28/12/2007	Variation to change company name from Evotec (Scotland) Limited to: Aptuit (Glasgow) Limited.
30/09/2008	Variation: Add Mr Jim Boaden as a new QP.
28/10/2008	Update licence to EUDRA GMP format.
19/06/2009	Variation: 1. Remove Cheynee Whipps as L/H and QP. 2. Add Mrs J Coleman as an additional QP. 3. Change L/H contact to Mr A Baillie. 4. Change Site name for site id 388368 to Gen-Probe Life Sciences.
26/10/2009	Variation to add Mr P Graham as a QP to site 92248.
20/12/2010	Variation to (1) Add Mr Richard J Smalley as a QP for Site 92248 (2) Replace Ms J Colman with Mr Alan Parker as the Licence Holder Contact (3) Add Piramal Healthcare UK Limited as a Contract Laboratory

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20/05/2011	Variation to remove Mr Jim Boaden as QP from site 92248 and add Aptuit (Oxford) Limited as an additional contract lab site.
02/08/2011	Variation to remove Jane Colman as a QP, replace Alan Parker with Chris Bland, and remove 2.2.3.5; 2.2.3.6; 2.2.3.7 and 2.2.4.3 to not authorised.
08/11/2013	Variation: Change LHC and QC to Mr M Reid, remove Richard Smalley as QP, remove Mr P Fullerton as QC, remove solids & implants and semi-solids.
09/05/2016	Variation to: - change site name for site 92248 from Aptuit (Glasgow) Limited to Albany Molecular Research Inc. (Glasgow) Limited - change site name for site 388368 from GEN-PROBE LIFE SCIENCES to Hologic Limited trading as Tepnel Pharma Services - replace Mr Chris Bland with Mr Martin Reid as contact person on site 92248 - remove SGS M-SCAN LIMITED (site 87471) as contract lab - remove APTUIT (OXFORD) LIMITED (site 839548) as contract lab - update site functions for site 92248
10/06/2016	Variation to change the company name from Aptuit (Glasgow) Limited to ALBANY MOLECULAR RESEARCH (GLASGOW) LIMITED
15/08/2016	Variation: Add Contract Laboratory (FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LIMITED)
09/03/2017	Variation: Add Mr Martin James Reid as QP (site 92248)
13/03/2017	Internal Variation: Add Mr Martin James Reid as QP (site 92248)
08/06/2018	Variation: Add Melbourn Scientific Limited as a contract laboratory; change address and site contact of Wickham Laboratories limited contract laboratory; add Manufacture of other terminally sterilised prepared products to site 92248
21/06/2019	Variation to add site 38651 - contract laboratory
07/05/2020	Variation to replace Mr Paul Graham with Mrs Clare Edwards as QP

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Medicines & Healthcare products Regulatory Agency

MHRA

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MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 3

ANNEX 2 - SITE INFORMATION

SCOPE OF AUTHORISATION

Name and address of site:

SITE NAME:	ALBANY MOLECULAR RESEARCH INC. (GLASGOW) LIMITED
ADDRESS:	BLOCK K, TODD CAMPUS, WEST OF SCOTLAND SCIENCE PARK, ACRE ROAD, GLASGOW, G20 0XA, UNITED KINGDOM
MHRA SITE NUMBER:	92248

Type of products handled

Human Investigational Medicinal Products for phase I, II, III clinical trials (optional)

Authorised operations

Manufacturing Operations of Investigational Medicinal Products (according to Part 1)	Authorised
Importation of Investigational Medicinal Products (according to Part 2)	Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

ANNEX 2 – SITE INFORMATION (continued)

Part 1 – MANUFACTURING OPERATIONS OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;
- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1	**Sterile Investigational Medicinal Products**	**Manufacture**
1.1.1	**Aseptically prepared (processing operations for the following dosage forms)**	
	1.1.1.1 Large volume liquids	Authorised
	1.1.1.2 Lyophilisates	Authorised
	1.1.1.3 Semi-solids	Not Authorised
	1.1.1.4 Small volume liquids	Authorised
	1.1.1.5 Solids and implants	Not Authorised
	1.1.1.6 Other aseptically prepared products	Not Authorised

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MHRA

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1.1.2	***Terminally Sterilised (processing operations for the following dosage forms)***	**Manufacture**
	1.1.2.1 Large volume liquids	Authorised
	1.1.2.2 Semi-solids	Not Authorised
	1.1.2.3 Small volume liquids	Authorised
	1.1.2.4 Solids and implants	Not Authorised
	1.1.2.5 Other terminally sterilised prepared products Implant for Injection using Glide Technologies Solid Dose Injector System;; Drug loaded, lyphilised polymer beads for intra-arterial injection	Authorised
1.1.3	***Batch certification***	Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

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1.2	Non-sterile investigational medicinal products	Manufacture
1.2.1	***Non-Sterile Products (processing operations for the following dosage forms)***	
	1.2.1.1 Capsules, hard shell	Not Authorised
	1.2.1.2 Capsules, soft shell	Not Authorised
	1.2.1.3 Chewing gums	Not Authorised
	1.2.1.4 Impregnated matrices	Not Authorised
	1.2.1.5 Liquids for external use	Authorised
	1.2.1.6 Liquids for internal use	Authorised
	1.2.1.7 Medicinal gases	Not Authorised
	1.2.1.8 Other solid dosage forms	Authorised
	1.2.1.9 Pressurised preparations	Not Authorised
	1.2.1.10 Radionuclide generators	Not Authorised
	1.2.1.11 Semi-solids	Not Authorised
	1.2.1.12 Suppositories	Not Authorised
	1.2.1.13 Tablets	Not Authorised

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	1.2.1.14 Transdermal patches	Not Authorised
	1.2.1.15 Other non-sterile medicinal products	Not Authorised
1.2.2	***Batch certification***	Not Authorised

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MHRA

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1.3	Biological investigational medicinal products	Manufacture
1.3.1	***Biological medicinal products (list of product types)***	
	1.3.1.1 Blood products	Not Authorised
	1.3.1.2 Immunological products	Not Authorised
	1.3.1.3 Cell therapy products	Not Authorised
	1.3.1.4 Gene therapy products	Not Authorised
	1.3.1.5 Biotechnology products	Authorised
	1.3.1.6 Human or animal extracted products	Authorised
	1.3.1.7 Tissue Engineered Products	Not Authorised
	1.3.1.8 Other biological medicinal products *Proteins and Biologics derived from cell lines*	Authorised
1.3.2	***Batch certification***	
	1.3.2.1 Blood products	Not Authorised
	1.3.2.2 Immunological products	Not Authorised
	1.3.2.3 Cell therapy products	Not Authorised
	1.3.2.4 Gene therapy products	Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

	1.3.2.5 Biotechnology products	Not Authorised
	1.3.2.6 Human or animal extracted products	Not Authorised
	1.3.2.7 Tissue Engineered Products	Not Authorised
	1.3.2.8 Other biological medicinal products	Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

1.4	***Other investigational medicinal products or manufacturing activity*** (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when required by national legislation), medicinal gases, herbal or homeopathic products, bulk or total manufacturing, etc).	**Manufacture**
1.4.1	**Manufacture of:**	
	1.4.1.1 Herbal products	Not Authorised
	1.4.1.2 Homoeopathic products	Not Authorised
	1.4.1.3 Other Hormones, Cytotoxics/Cytostatics, Non-Cytotoxic Organic/Inorganic Chemically active.	Authorised
1.4.2	**Sterilisation of active substances/excipients/finished products:**	
	1.4.2.1 Filtration	Authorised
	1.4.2.2 Dry heat	Authorised
	1.4.2.3 Moist heat	Authorised
	1.4.2.4 Chemical	Not Authorised
	1.4.2.5 Gamma irradiation	Not Authorised
	1.4.2.6 Electron beam	Not Authorised
1.4.3	**Others**	Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

1.5	*Packaging*	Packaging
1.5.1	***Primary packing***	
	1.5.1.1 Capsules, hard shell	Not Authorised
	1.5.1.2 Capsules, soft shell	Not Authorised
	1.5.1.3 Chewing gums	Not Authorised
	1.5.1.4 Impregnated matrices	Not Authorised
	1.5.1.5 Liquids for external use	Not Authorised
	1.5.1.6 Liquids for internal use	Not Authorised
	1.5.1.7 Medicinal gases	Not Authorised
	1.5.1.8 Other solid dosage forms	Not Authorised
	1.5.1.9 Pressurised preparations	Not Authorised
	1.5.1.10 Radionuclide generators	Not Authorised
	1.5.1.11 Semi-solids	Not Authorised
	1.5.1.12 Suppositories	Not Authorised
	1.5.1.13 Tablets	Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

	1.5.1.14 Transdermal patches	Not Authorised
	1.5.1.15 Other non-sterile medicinal products	Not Authorised
1.5.2	**Secondary packing**	Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

1.6	**Quality control testing**	
	1.6.1 Microbiological: sterility	Not Authorised
	1.6.2 Microbiological: non-sterility	Authorised
	1.6.3 Chemical/Physical	Authorised
	1.6.4 Biological	Authorised

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations:

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 MHRA Site No: 92248 VERSION: 23

ANNEX 5/6 – SITE INFORMATION (continued)

Personnel

Person Number	Name	Personnel Type			
		QP	TQP	PM	QC
1237698	Dr I Macgilp	No	No	Yes	No
10140739	Mr Martin James Reid	Yes	No	No	Yes
3065514	Mrs Clare Edwards	Yes	No	No	No

Key to Roles:

QP – Qualified Person
TQP – Transitional Qualified Person
PM – Production Manager/Supervisor
QC – Person responsible for Quality Control

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 VERSION: 23

ANNEX 4 – CONTRACT LABORATORIES

MHRA SITE NUMBER:	LABORATORY NAME:	ADDRESS:
10933	PIRAMAL HEALTHCARE UK LIMITED	EARLS ROAD, GRANGEMOUTH, FK3 8XG, UNITED KINGDOM
10934	FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LIMITED	BELASIS AVENUE, BILLINGHAM, TS23 1LH, UNITED KINGDOM
38651	READING SCIENTIFIC SERVICES LIMITED	READING SCIENCE CENTRE, WHITEKNIGHTS CAMPUS, PEPPER LANE, READING, RG6 6LA, UNITED KINGDOM
336740	MELBOURN SCIENTIFIC LIMITED TA INTERTEK MELBOURN	SAXON WAY, MELBOURN, ROYSTON, SG8 6DN, UNITED KINGDOM
388368	HOLOGIC LIMITED TA TEPNEL PHARMA SERVICES	APPLETON PLACE, APPLETON PARKWAY, LIVINGSTON, EH54 7EZ, UNITED KINGDOM
5994535	WICKHAM LABORATORIES LIMITED	HOEFORD POINT, BARWELL LANE, GOSPORT, PO13 0AU, UNITED KINGDOM

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Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19124 VERSION: 23

ANNEX 9 – STORAGE SITES

MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
92248	ALBANY MOLECULAR RESEARCH INC. (GLASGOW) LIMITED	BLOCK K, TODD CAMPUS, WEST OF SCOTLAND SCIENCE PARK, ACRE ROAD, GLASGOW, G20 0XA, UNITED KINGDOM

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The GMP certification of Albany Molecular Research Inc. (Glasgow) Limited [AMRI] is provided below. AMIR changed its company to Curia (Scotland) Limited in July 2021.

Medicines & Healthcare products Regulatory Agency

MHRA

Certificate No: UK MIA(IMP) 19124 Insp GMP/IMP 19124/92248-0007

Medicines and Healthcare products Regulatory Agency

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 15 of Directive 2001/20/EC.

The competent authority of the United Kingdom confirms the following:

The manufacturer	ALBANY MOLECULAR RESEARCH INC. (GLASGOW) LIMITED
Site address	BLOCK K TODD CAMPUS WEST OF SCOTLAND SCIENCE PARK ACRE ROAD GLASGOW G20 0XA UNITED KINGDOM

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. MIA(IMP) 19124 in accordance with Art. 13 of Directive 2001/20/EC transposed in the following national legislation: The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 25/02/2019, it is considered that it complies with the principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field.

This certificate is only valid when presented with all pages and both parts 1 and 2.

The authenticity of this certificate may be verified in EudraGMDP. If it does not appear please contact the issuing authority.

Medicines & Healthcare products Regulatory Agency

MHRA

Certificate No: UK MIA(IMP) 19124 Insp GMP/IMP 19124/92248-0007

Part 2

Human Investigational Medicinal Products for phase I, II, III clinical trials

1. MANUFACTURING OPERATIONS

1.1 Sterile products

1.1.1 Aseptically prepared (processing operations for the following dosage forms)

1.1.1.1 Large volume liquids
1.1.1.2 Lyophilisates
1.1.1.4 Small volume liquids

1.1.2 Terminally sterilised (processing operations for the following dosage forms)

1.1.2.1 Large volume liquids
1.1.2.3 Small volume liquids
1.1.2.5 Other terminally sterilised prepared products
Implant for Injection using Glide Technologies Solid Dose Injector System;; Drug loaded, lyphilised polymer beads for intra-arterial injection

1.2 Non-sterile products

1.2.1 Non-sterile products (processing operations for the following dosage forms)

1.2.1.5 Liquids for external use
1.2.1.6 Liquids for internal use
1.2.1.8 Other solid dosage forms

1.3 Biological medicinal products

1.3.1 Biological medicinal products

1.3.1.5 Biotechnology products
1.3.1.6 Human or animal extracted products
1.3.1.8 Other biological medicinal products
Proteins and Biologics derived from cell lines

1.4 Other products or manufacturing activity

1.4.1 Manufacture of

1.4.1.3 Other
Hormones, Cytotoxics/Cytostatics, Non-Cytotoxic Organic/Inorganic Chemically active.

1.4.2 Sterilisation of active substances/excipients/finished product

1.4.2.1 Filtration
1.4.2.2 Dry heat
1.4.2.3 Moist heat

1.5 Packaging

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1.5.2 Secondary packaging

1.6 Quality control testing

1.6.2 Microbiological: non-sterility
1.6.3 Chemical/physical
1.6.4 Biological

2. IMPORTATION OF MEDICINAL PRODUCTS

2.1 Quality control testing of imported medicinal products

Not Authorised

2.2 Batch certification of imported medicinal products

Not Authorised

2.3 Other importation activities

Not Authorised

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MHRA

Certificate No: UK MIA(IMP) 19124 Insp GMP/IMP 19124/92248-0007

3. MANUFACTURING OPERATIONS

3.1 Manufacture of Active Substance by Chemical Synthesis
Not Authorised

3.2 Processing Activities of Active Substance from Natural Sources
Not Authorised

3.3 Manufacture of Active Substance using Biological Processes
Not Authorised

3.4 Manufacture of sterile active substance
Not Authorised

3.5 General Finishing Steps
Not Authorised

3.6 Quality Control Testing
Not Authorised

4 Other Activities
Not Authorised

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Medicines & Healthcare products Regulatory Agency

MHRA

Certificate No: UK MIA(IMP) 19124 Insp GMP/IMP 19124/92248-0007

Any restrictions or clarifying remarks related to the scope of this certificate:

This certificate is issued based on a desk-based assessment of GMP compliance information provided by the manufacturer. A risk-based site inspection programme remains in force.

1. Building(s)/Area(s)

   N/A

2. Room(s)

   N/A

3. Line(s) Equipment(s)

   N/A

4. QC testing

   N/A

5. Medicinal Product(s)/IMP(s)

   N/A

Name of the authorised person of the Competent Authority of the United Kingdom

Dr A J Gray
Head of Inspectorate
inspectionplanning@mhra.gov.uk

Date: 25/02/2019

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AMRI's inspection and approval process for incoming IMP vials is provided below.

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9.2 Appendix 2 – ISO 2859-1, Sample Plan – General Inspection Level I Used

Table 1 - Sample size code letters (see 10.1 and 10.2)

Lot size	Special inspection levels				General inspection levels		
	S-1	S-2	S-3	S-4	I	II	III
2 to 8	A	A	A	A	A	A	B
9 to 15	A	A	A	A	A	B	C
16 to 25	A	A	B	B	B	C	D
26 to 50	A	B	B	C	C	D	E
51 to 90	B	B	C	C	C	E	F
91 to 150	B	B	C	D	D	F	G
151 to 280	B	C	D	E	E	G	H
281 to 500	B	C	D	E	F	H	J
501 to 1 200	C	C	E	F	G	J	K
1 201 to 3 200	C	D	E	G	H	K	L
3 201 to 10 000	C	D	F	G	J	L	M
10 001 to 35 000	C	D	F	H	K	M	N
35 001 to 150 000	D	E	G	J	L	N	P
150 001 to 500 000	D	E	G	J	M	P	Q
500 001 and over	D	E	H	K	N	Q	R

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9.3 Appendix 3 – ISO 2859-1, Single Sampling Plans for Normal Inspection

Table 2-A — Single sampling plans for normal inspection (Master table)

Sample size code letter	Sample size	Acceptance quality limit, AQL, in percent nonconforming items and nonconformities per 100 items (normal inspection)																									
		0,010	0,015	0,025	0,040	0,065	0,10	0,15	0,25	0,40	0,65	1,0	1,5	2,5	4,0	6,5	10	15	25	40	65	100	150	250	400	650	1 000
		Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re
A	2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↓	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31
B	3	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45
C	5	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑
D	8	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑	↑
E	13	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑	↑	↑
F	20	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑
G	32	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑
H	50	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑
J	80	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑
K	125	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
L	200	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
M	315	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
N	500	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
P	800	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Q	1 250	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
R	2 000	↑	↑	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

↓ = Use the first sampling plan below the arrow. If sample size equals, or exceeds, lot size, carry out 100 % inspection.
↑ = Use the first sampling plan above the arrow.
Ac = Acceptance number
Re = Rejection number

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Date Approved:	29 Oct 20	

3.1.A.2 Adventitious agents safety evaluation

The API and the excipients used in the formulation are not of human or animal origin.

TSE agents

The TSE/BSE statement from the API manufacturer, Cambrex Profarmaco Milano S.r.l. is provided below.

Cambrex

January 2020

TO WHOM IT MAY CONCERN

STATEMENT

RE: Cysteamine Bitartrate BSE/TSE

We, Cambrex Profarmaco Milano S.r.l., addressed in Paullo (Milano, Italy) – Via Curiel 34, herewith confirm that for the manufacture of **Cysteamine Bitartrate** produced in our Plant of Paullo no raw material derived from cattle, sheep, goats and cow is used. **Cysteamine Bitartrate** complies with requirement of TSE/BSE "Note for guidance EMEA/410/01", and with the code of Federal Regulations of the "USFDA – 9CFR part 94.23 pertaining to the importation of Gelatin from Bovines".

We also confirm:

- that material is not of animal origin and it has not been produced using reagents / intermediates of animal origin;
- That the outsourced starting material of **Cysteamine Bitartrate** is free from BSE/TSE (according to the declaration of our suppliers)
- that no material of human origin is used in the manufacturing process of **Cysteamine Bitartrate**.

Yours Faithfully,
Cambrex Profarmaco Milano S.r.l.

Dr. Luigi Bellone
QA Manager
24/01/2020

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VAT: IT 11413690154 • R.E.A.: MI 1465184
Codice fiscale/Reg. Impr. MI: 02330040243

Viral safety

Not applicable

Other adventitious agents

Not applicable

3.1.A.3 Novel excipients

None involved.

3.1.A.4 Solvents for reconstitution and diluents

Not applicable.