PACKMaN

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

Ketamine 15mg/ml (2ml ampoules containing 1ml)

Morphine 10mg/ml (2ml ampoules containing 1ml)

Version No.:	2.0
Date:	15 March 2021
Sponsor:	The University of Warwick
Full Title:	Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma : PACKMaN
EudraCT No:	2020-000154-10

TABLE OF CONTENTS

INTRODUCTION

The PACKMaN trial is a multi-centre, pragmatic, controlled, blinded trial investigating if ketamine is superior to morphine at reducing pain in adults with severe pain due to acute traumatic injury.

The investigational medicinal products are ketamine 15mg/ml solution for injection (2ml ampoules containing 1ml) and morphine 10mg/ml solution for injection (2ml ampoules containing 1ml). All investigational medicinal products are manufactured according to EU GMP and labelled according to Annex 13 guidelines in a trial-specific way.

A. KETAMINE 15MG/ML (2ML AMPOULES CONTAINING 1ML)

S DRUG SUBSTANCE

Ketamine hydrochloride Ph. Eur. is manufactured by CU Chemie Uetikon GmbH.

CU Chemie Uetikon GmbH hold a Certificate of Suitability for the manufacture of Ketamine Hydrochloride, No. R1-CEP 2005-281-Rev 00 (refer to Attachment 2).

Name of holder:

CU CHEMIE UETIKON GMBH
Raiffeisenstrasse 4
Germany-77933 Lahr

Site of production:

CU CHEMIE UETIKON GMBH
Raiffeisenstrasse 4
Germany-77933 Lahr

P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

P.1 Description and Composition

The product contains Ketamine hydrochloride as the active pharmaceutical ingredient, in aqueous solution at a concentration of 17.4mg in 1ml, equivalent to 15mg per 1mL of Ketamine base. The product is presented as a sterile, clear, colourless solution as below.

KET01 - 1mL in a 2mL Type 1 glass ampoule

One 1mL dose of Ketamine 15mg/mL Solution contains the following:

Component	**Function**	**Amount in 1mL**	**Ref to Std**
Ketamine hydrochloride	Therapeutic agent	17.4mg^{+}	Ph. Eur
Sodium Chloride	Osmotic agent	9mg	Ph. Eur
Distilled water	Solubiliser, Vehicle	To 1mL	Ph. Eur

$^{+}$ = adjusted for purity and loss on drying

P.2 Pharmaceutical Development

P.2.1 Formulation Development

Ketamine hydrochloride is commonly used in injections and infusions (ref Katalar PL 00057/0529) due to the increased aqueous solubility over Ketamine base. Sodium chloride is required as an osmotic agent for injections.

P.2.2. Overages

No overages have been applied to the product. The amount of Ketamine hydrochloride is adjusted for the hydrochloride salt and the potency of the batch of material (purity by assay and water content) to provide a dose of Ketamine base in the solution at 15mg in 1mL.

P.2.3. Physicochemical and biological properties

Ketamine is a cyclohexanone derivative with analgesic and anesthetic properties. Although its mechanism of action is not well understood, ketamine appears to exert complex pharmacological actions including inhibition of biogenic amine uptake, binding to opioid receptors, and inhibition of N-methyl D-aspartate (NMDA) receptors. Because of the involvement of spinal NMDA receptors in the process of central sensitization, this agent may reduce pain perception and induce sedation.
(https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C61797)

P.3 Manufacture

P.3.1 Manufacturer(s)

The manufacture of the ampoules will be carried out by:

> Calderdale and Huddersfield NHS Foundation Trust trading as Huddersfield Pharmacy Specials (HPS)
>
> Manufacturing site: Acre Mills, Gate 2, School Street West, Lindley, Huddersfield, HD3 3ET, UK
>
> MIA(IMP) Authorisation: MIA(IMP) 19055

A copy of the MIA (IMP) authorisation has been included as part of this submission (Attachment 1).

P.3.2 Batch Formula

Batch size: Approximately 2 litres of solution will be prepared per batch.

1 litre contains:

Excipient	**Amount**
Ketamine hydrochloride	17.2952g
Sodium Chloride	9.0g
Water for injection	q.s.1L

P.3.3 Description of Manufacturing Process and Process Controls

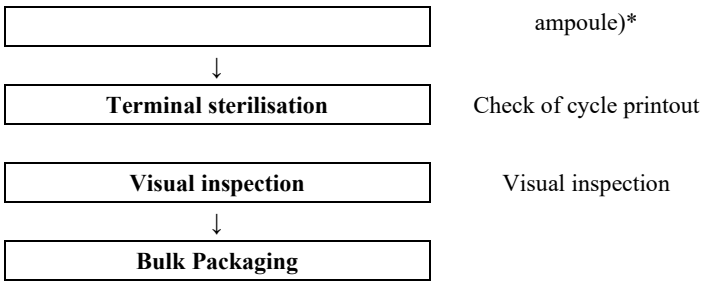
Description

1. Add water for injection to the main vessel
2. Add the Ketamine hydrochloride and mix until dissolved
3. Add the sodium chloride and mix until dissolved
4. Make to volume with water for injection
5. Record the pH
6. Fill into ampoules
7. Sterilise by autoclave

Flow chart

Sterile Manufacture

	In Process Controls	Environment
The Excipient and API are weighed	Check of balance	Grade C
↓		
Dissolution of API in WFI	Visual check dissolved	Grade C
↓		
Dissolution of exipient in WFI	Visual check dissolved	Grade C
↓		
Make to Volume in WFI	Visual volume check	Grade C
↓		
Verify pH is in range 4.0 – 5.0	Check of pH meter	Grade C
↓		
Dissolution of exipient in WFI	Visual check dissolved	Grade C
↓		
Sterile filtration 0.2 µm	Pre-filtration bioburden (<10cfu/100 ml) Filter integrity test	Grade A
↓		
Dispensing	Filling weight (1.3mL ± 0.1mL per	Grade A



P.3.4 Control of Critical Steps and Intermediates

No critical steps have been identified in the manufacturing process.

A visual check of the solution is performed after mixing to ensure full dissolution of the API/excipient prior to continuation to the next step.

The pH of the final solution is checked to verify that it is within the required range of pH4.0 – 5.0

P.3.5 Process Validation and/or Evaluation

Process Validation is not required at this stage of the application.
The method of sterilization by autoclave cycle has been fully validated for the proposed container closure system. Sterility is assured by QC evaluation of the Drug Product as per pharmacopoeia.

P.4 Control of Excipients

P.4.1 Specifications

Water for Injection in bulk is produced by the drug product manufacturer by distillation. The water system is qualified and monitored on a scheduled basis in accordance with EU GMP and the Ph. Eur.

Excipient	**Reference to standard**
Sodium Chloride	Ph Eur

P.4.5 Excipients of Animal or Human Origin

Excipients are not derived from animal sources and hence there is no BSE/TSE risk regarding the used materials.

P.4.6 Novel Excipients

Not applicable

P.5 Control of the Drug Product

P.5.1 Specifications

Test	**Method**	**Acceptance Criteria**
Examination	Visual Inspection	A clear, colourless to pale yellow solution free from particulate contamination
pH	BP Appendix V L (Ph Eur 2.2.3)	3.5 – 5.5
Identification of Ketamine	HPLC (Assay of Ketamine and Known/Unknown Related substances) BP Appendix III D (Ph Eur 2.2.29)	1. Retention time comparison with a reference standard 2. UV Spectral Comparison with a reference standard
Assay of Ketamine		14.25 – 15.75mg/mL
Known/Unknown Related Substances		Not greater than 0.5% wrt API With not more than one >0.25% wrt API
Total Known/Unknown Related Substances (%wrt API)		Not greater than 1.0% wrt API
Sterility Test	BP Appendix XVI A (Ph Eur 2.6.1)	Pass
BET	BP Appendix XIV C (Ph Eur 2.6.14)	<17.0 EU/mg
Sub-visible particle count	BP Appendix XIII A (Ph Eur 2.9.19)	10µm ≤6000/container 25µm ≤600/container

P.5.2 Analytical Procedures

Ph. Eur. and BP methods are used throughout with the following exception.

<u>Assay of Ketamine hydrochloride, known and unknown related substances by HPLC-UV</u>

Note with respect to the HPLC method

In the future, chromatographic conditions may be adjusted to attain or optimize system performance and suitability. Equivalent chromatographic columns and related equipment

may be substituted if found suitable. Quantities proportionally larger or smaller than the specified weights and volumes of samples, standards, and reagents may be used. Subsequent steps, such as dilution, may be adjusted accordingly to yield concentrations equivalent to those specified. As required, calculation of results may be corrected to account for changes in weights and/or volumes. However, changes to the method may only be incorporated after successful completion of the applicable validation.

Equipment: A suitable HPLC system fitted with a Diode Array UV detector.

Chromatographic conditions:

Column	ACE Excel 3 Super C18 125 x 4.6 mm, Part number: EXL-1111-1246u
Mobile phase	Dissolve 1.36 g potassium dihydrogen phosphate in 650mL water and add 1 mL triethylamine and 350 mL acetonitrile. Mix well and sonicate for 10 minutes before use.
Flow Rate	1.5 mL/min
Sample volume	15 uL
Oven Temperature	40ºC
UV Wavelength	248 nm
Run Time	13 minutes for standards and 30 minutes for samples
Peak width	0.5
Bandwidth	1
Wash Solvent	50% Methanol

Run mobile phase for at least 15 minutes to allow column to equilibrate.

Preparation of Calibration Standard Solution:
Weigh accurately 0.15 - 0.19 g of ketamine hydrochloride reference standard into a 50 mL volumetric flask and dissolve in water, dilute to volume with water.

To be prepared in duplicate to provide a recovery standard

Preparation of Test Sample Solution (0.3%w/v):
Add by pipette 2.0 mL of well mixed sample into a 10 mL volumetric flask and dissolve in water. Dilute to volume with water and mix well.

Preparation of 0.5% Limit Test Solution:
Dilute 1.0mL of Calibration Standard Solution to 200mL with water.

Preparation of 0.25% Limit Test Solution:
Dilute 5.0mL of 0.5% Limit Test Solution to 10mL with water.

Preparation of 0.1% Limit Test Solution:
Dilute 2.0mL of 0.5% Limit Test Solution to 10mL with water.

Analytical Solution Stability:
Standard solutions are stable for 21 days when stored at ambient temperature.

Calculations

All standard weights are corrected for purity
A factor is shown in each calculation to convert to the correct salt form.

Corrected standard weight for Ketamine (mg/mL) =

$$\frac{\text{Standard weight} \times 1000 \times \text{Purity} \times 237.7}{50 \times 100 \times 274.2}$$

Calculation of Ketamine =

$$\frac{\text{Corrected Standard weight} \times \text{area ketamine in sample} \times 100}{\text{Area ketamine in std}} = \text{mg/mL ketamine}$$

Calculation of Ketamine Related Substances =

$$\frac{\text{Corrected Standard weight} \times \text{area related substance in sample} \times 1000}{\text{Area ketamine in std} \times 5} = \%\text{w/v ketamine}$$

The expected retention time for each analyte is below:

Component	Approx. Retention Time
Ketamine	9.3 mins
Impurity A	10.3 mins

Figure P.5.2.1: Chromatogram of atypical Calibration Standard injection

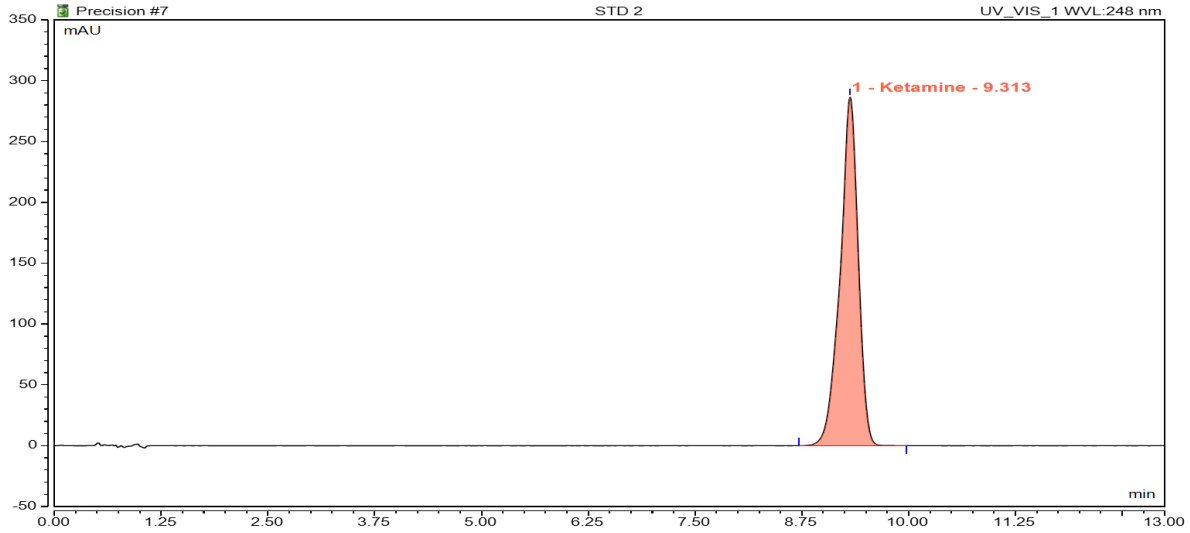


Figure P.5.2.2: Chromatogram of a typical test sample injection:

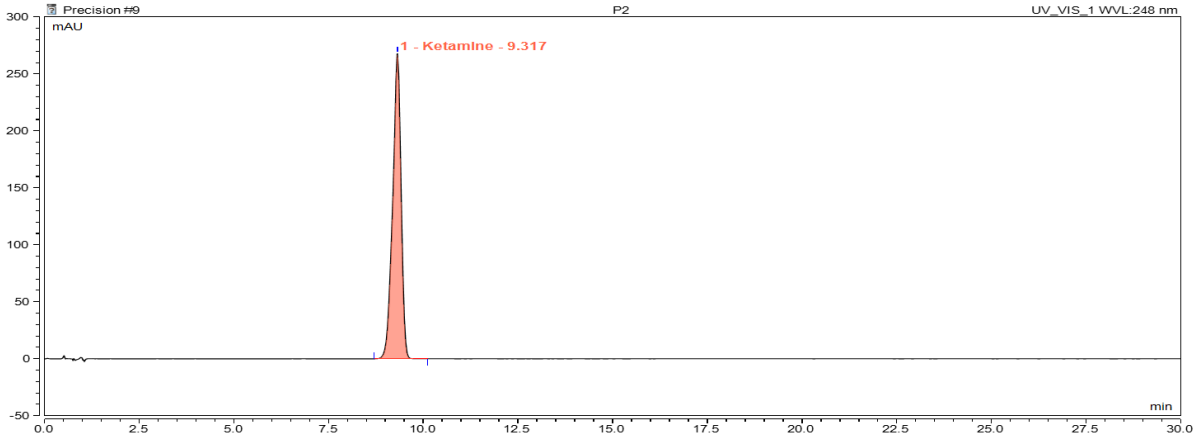
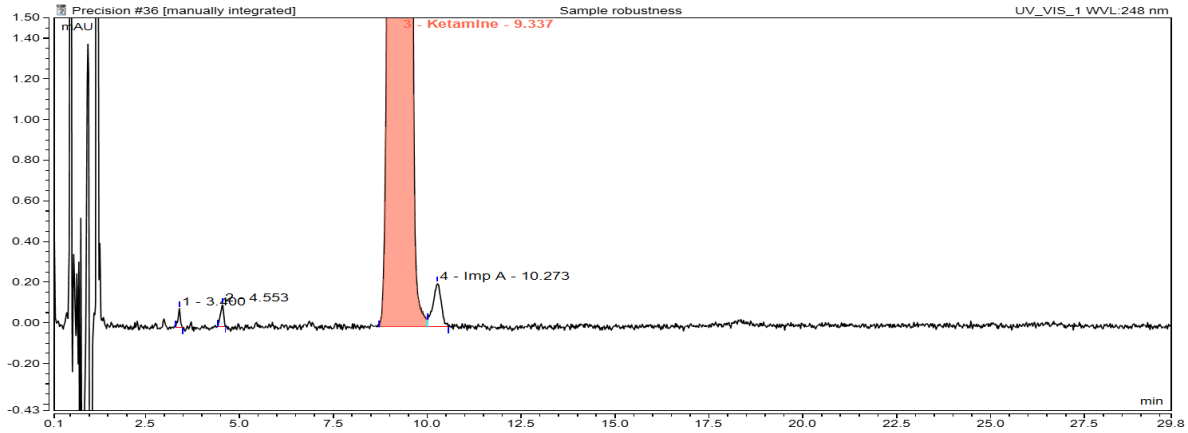


Figure P.5.2.3 Baseline scaled chromatogram of a spiked sample demonstrating the retention time of known impurity.



P.5.3 Validation of Analytical Procedures

The validation of analytical procedures is not required as they are taken from the European Pharmacopeia and British Pharmacopeia, if not stated otherwise below.

Parameter/Assessment	**Acceptance criteria**	**Result**
Specificity	• The peak due to Ketamine hydrochloride must be free from interference • The minimum resolution between Ktamine hydrochloride and any other peak must be >1.5. • Peak purity of Ketamine hydrochloride in all unadulterated samples should be between 98.0 – 102.0 % of the standard. • The UV spectra of Ketamine hydrochloride must be concurrent between sample and standard.	Specificity confirmed
Linearity (Samples of Ketamine	Correlation Co-efficient R^2 >99.9%	R^2 = 100.00

hydrochloride at 0.05-120%)		
Accuracy (spiked samples 0.05, 80, 100 and 120%; 6 repeats)	Recovered amounts should be as below: At 0.05%, 0.1%, within 85.0 – 115.0% At 1.0% within 90.0 – 110.0% At 80,100, 120% - within 98.0-102.0%	Accuracy confirmed for Ketamine hydrochloride
Precision (repeatability) a) 6 replicates tested in duplicate, b) 10 repeats of same sample	a) %RSD ≤2.0 b) %RSD ≤1.0	a) 0.8%RSD b) 0.1%RSD

Limit of Detection and Quantification of Ketamine hydrochloride

Ketamine can be easily quantified at 0.05% of nominal concentration. Signal:Noise Ratios below are taken from the accuracy solutions at 0.05% which is below the reporting threshold of the specification.

Identification	**Signal to noise ratio**			**Mean**
	Injection 1	**Injection 2**	**Injection 3**	
0.05% accuracy 1	10.3	11.3	11.3	11.5
0.05% accuracy 2	12.3	10.3	11.0	
0.05% accuracy 3	11.3	12.2	13.1	
Acceptance Criteria: >10				
All acceptance criteria met.				

Intermediate Precision is not required at this stage of the application.

P.5.3.1 Validation of the Test for Bioburden

Not required at this stage of the application.

P.5.3.2 Validation of the Test for Sterility

The method validation report has been included as Attachment 5.

P.5.3.3 Validation of the Test for Bacterial Endotoxins

The method validation report has been included as Attachment 6.

P.5.4 Batch Analysis

The below batch is representative of a batch intended for use in the proposed clinical trial.

Test	**Batch no:**	300218X
	Manufacturing Date:	18Feb2020
	Batch size:	2.5L (567 units sub batch)
	Acceptance Criteria	**Result**
Examination	A clear, colourless to pale yellow solution free from particulate contamination	Complies
pH	3.5 – 5.5	4.5
Identification of Ketamine	1. Retention time comparison with a reference standard 2. UV Spectral Comparison with a reference standard	1. Complies 2. Complies
Assay of Ketamine	14.25 – 15.75mg/mL	
Known/Unknown Related Substances	Not greater than 0.5% wrt API With not more than one >0.25% wrt API	Complies
Total	Not greater than 1.0% wrt API	Complies
Sterility Test	Pass	Pass
BET	<17.0 EU/mg	
Particle counts	10µm ≤6000/container 25µm ≤600/container	9.1 0.4

P.7 Container Closure System

Primary Packaging

2ml Type 1 Fiolax clear Form D glass ampoules according to Ph. Eur. 3.2.1.

P.8 Stability

Storage Conditions:

Store in a dry place. Protect from light.

Shelf-life:

Based on historical data of existing ketamine products an initial expiry of 12 months will be assigned for Ketamine 15mg/mL in 2mL glass ampoules containing 1.2mL with a rolling program to extend the shelf-life to 24 months from data available via an ongoing stability study plan (see 'Shelf-life Extension Program' below).

The preparation is to be used immediately after opening so no in-use stability data will be presented.

Samples from three batches of ampoules will be included in a supporting ongoing stability study program with analysis performed as described below. Data from this study will be reviewed at each time point to verify the predicted shelf life of 24 months.

Stability control

The stability study protocol has been designed to provide assurance of ongoing stability:

Product Code	KET01S	**Batch number**	300218X	**DOM**	18Feb2020
Product Name	Ketamine injection				
Strength	15mg/mL		**Pack size**	1mL in 2mL ampoule	
Aim of Study					
Development batch to perform stability study in support of Packman Clinical Trial C013					
Duration of Stability Study	18M				
Timepoints required	0,1,2,3,6,9,12, 18, 24M				
Storage Condition(s)	25°C/60%RH, 30°C/65%RH, 40°C/75%RH				

Testing Requirements

Test	**Description**
(a)	Physical (appearance)
(b)	pH
(c)	Assay of Ketamine and Related Substances
(d)	Sterility
(e)	Particle Counts
(f)	Bacterial Endotoxins

Timepoints No. of samples to pull (testing requirements in brackets)

	T=0	**1M**	**2M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**
5°C	97 (a – f)								
25°C				12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)	82 (a-e)
30°C				12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)		
40°C		12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)				

Specifications are as stated in P.5.1

Shelf-life Extension Program

The initial 12 months expiry may be extended during the Clinical Trial based on the results of the stability study performed on a test batch. In the extension, extrapolation will be used requiring real-time data of ketamine assay and degradation products before an expiry is set as follows:

Real-time stability data available	**Proposed shelf-life**
3 months at accelerated conditions (40°C/75%RH)	12 months
12 months at ambient temperatures (25°C/60%RH)	24 months

The specification used will be the same as the Release analysis. Shelf-life will not be extended if the trend analysis performed according to ICH Q1E shows that the specification at the end of shelf-life is not met.

Stability results available at the time of submission are included in Attachment 9.

B. MORPHINE 10MG/ML (2ML AMPOULES CONTAINING 1ML)

S DRUG SUBSTANCE

Morphine sulfate Ph. Eur. is manufactured by Johnson Matthey, now known as MACFARLAN SMITH LIMITED GB EH11 2QA Edinburgh.

Johnson Matthey manufacture Morphine sulfate Ph. Eur. in accordance with EDQM Certificate of Suitability No. R1-CEP 2001-239-Rev 06, a copy of which is included in the application (Attachment 3).

P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

P.1 Description and Composition

The product contains Morphine sulfate as the active pharmaceutical ingredient, in aqueous solution at a concentration of 10mg in 1ml. The product is presented as a sterile, clear, colourless solution as below.

MOR19S - 1mL in a 2mL Type 1 glass ampoule

One 1mL dose of Morphine sulfate 10mg/mL solution contains the following:

Component	**Function**	**Amount in 1mL**	**Ref to Std**
Morphine sulfate	Therapeutic agent	10mg^{+}	Ph. Eur
Sodium Chloride	Osmotic agent	9mg	Ph. Eur
Disodium edetate	Chelating agent	1mg	Ph. Eur
Distilled water	Solubiliser, Vehicle	To 1mL	Ph. Eur

$^{+}$ = adjusted for purity and loss on drying

P.2 Pharmaceutical Development

Morphine sulfate is commercially available as an injection in various strengths and pack sizes. It was originally licenced by Bristol Laboratories Limited and a number of generic equivalents are available.

Morphine is one of a group of medicines called opioid analgesic, which act at specific points in the brain and nervous tissue to alter the patient's sensitivity to pain.

P.3 Manufacture

P.3.1 Manufacturer(s)

The manufacture of the ampoules will be carried out by:

Calderdale and Huddersfield NHS Foundation Trust trading as Huddersfield Pharmacy Specials (HPS)

Manufacturing site: Acre Mills, Gate 2, School Street West, Lindley, Huddersfield, HD3 3ET, UK

MIA(IMP) Authorisation: MIA(IMP) 19055

A copy of the MIA(IMP) authorisation has been included as part of this submission (Attachment 1).

P.3.2 Batch Formula

Batch size: Approximately 2 litres of solution will be prepared per batch.

1 litre contains:

Excipient	**Amount**
Morphine sulfate	10.0g
Sodium Chloride	9.0g
Disodium edetate	1.0g
Distilled water	q.s.1L

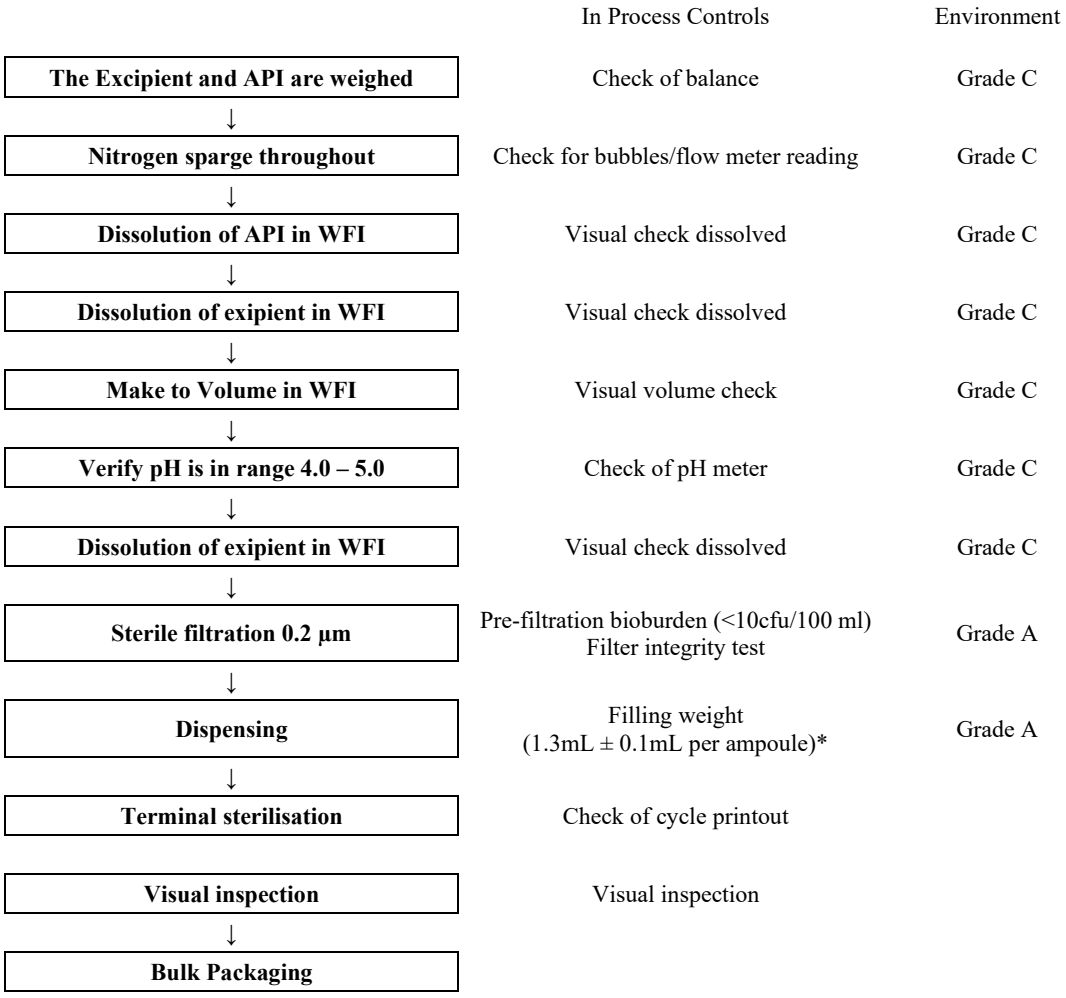
P.3.3 Description of Manufacturing Process and Process Controls

Description

1. Add water for injection to the main vessel
2. Sparge the vessel with nitrogen throughout
3. Add the Morphine Sulfate and mix until dissolved
4. Add the sodium chloride and mix until dissolved
5. Add the disodium edetate and mix until dissolved
6. Make to volume with water for injection
7. Record the pH
8. Fill into ampoules
9. Sterilise by autoclave

Flow chart

Sterile Manufacture



P.3.4 Control of Critical Steps and Intermediates

No critical steps have been identified in the manufacturing process.

A visual check of the solution is performed after mixing to ensure full dissolution of the API/excipient prior to continuation to the next step.

The pH of the final solution is checked to verify that it is within the required range of pH4.0 – 5.0

P.3.5 Process Validation and/or Evaluation

Process Validation is not required at this stage of the application.
The method of sterilization by autoclave cycle has been fully validated for the proposed container closure system. Sterility is assured by QC evaluation of the Drug Product as per pharmacopoeia.

P.4 Control of Excipients

P.4.1 Specifications

Water for Injection in bulk is produced by the drug product manufacturer by distillation. The water system is qualified and monitored on a scheduled basis in accordance with EU GMP and the Ph. Eur.

Excipient	**Reference to standard**
Sodium Chloride	Ph Eur
Disodium edetate	Ph Eur

P.4.5 Excipients of Animal or Human Origin

Excipients are not derived from animal sources and hence there is no BSE/TSE risk regarding the used materials.

P.4.6 Novel Excipients

Not applicable

P.5 Control of the Drug Product

P.5.1 Specifications

Test	**Method**	**Acceptance Criteria**
Examination	Visual Inspection	A clear, colourless to pale yellow solution free from particulate contamination
pH	BP Appendix V L (Ph Eur 2.2.3)	2.5 – 6.5
Identification of Morphine sulfate	HPLC (Assay of Ketamine and Known/Unknown Related substances) BP Appendix III D (Ph Eur 2.2.29)	1. Retention time comparison with a reference standard 2. UV Spectral Comparison with a reference standard
Assay of Morphine sulfate		9.5 – 10.5mg/mL
Codeine (Impurity A)		Not greater than 0.5%wrt API
Any other single Known Related Substance		Not greater than 0.2% wrt API
Any other single Unknown Related Substance		Not greater than 0.2% wrt API
Total Known/Unknown Related Substances (%wrt API)		Not greater than 2.0% wrt API
Sterility Test	BP Appendix XVI A (Ph Eur 2.6.1)	Pass
BET	BP Appendix XIV C (Ph Eur 2.6.14)	<17.0 EU/mg
Sub-visible particle count	BP Appendix XIII A (Ph Eur 2.9.19)	10µm ≤6000/container 25µm ≤600/container

P.5.2 Analytical Procedures

Ph. Eur. and BP methods are used throughout except where specified below:

Assay of Morphine sulfate, known and unknown related substances by HPLC-UV

Note with respect to the HPLC method

In the future, chromatographic conditions may be adjusted to attain or optimize system performance and suitability. Equivalent chromatographic columns and related equipment may be substituted if found suitable. Quantities proportionally larger or smaller than the specified weights and volumes of samples, standards, and reagents may be used. Subsequent steps, such as dilution, may be adjusted accordingly to yield concentrations equivalent to those specified. As required, calculation of results may be corrected to account for changes in weights and/or volumes. However changes to the method may only be incorporated after successful completion of the applicable validation.

Equipment: A suitable HPLC system fitted with a Diode Array UV detector.

Analytical column : Ace Excel 5 super C18 250 x 4.6mm

Chromatographic Conditions

Mobile phase A (1L)	1.35g sodium acetate trihydrate in water adjusted to pH 4.0 with glacial acetic acid					
Mobile phase B	Acetonitrile					
Gradient						
Time (min)	0	0.5	6.0	7.5	8.0	10.0
%B	7	7	20	20	7	7
Flow Rate	1.5 mL/min					
Sample volume	50µL					
Oven Temperature	40ºC					
UV Wavelength	285 nm					
Diode Array Detector	190 – 380 nm			Bunchwidth	1	
Run Time	10 minutes					
Wash Solvent	50:50 water:methanol					

Preparation of Stock Standard Solution:

Weigh accurately 0.095 - 0.105 g of Morphine Sulfate reference standard into a 100 mL volumetric flask and dissolve in water. Dilute to volume with water and mix well.

Preparation of Calibration Standard Solution:

Pipette 5.0mL of stock standard solution into a 50 mL volumetric flask and dilute to volume with water.

To be prepared in duplicate to provide a recovery standard.

Preparation of a Test Sample Solution:

Pipette 1.0 mL of well mixed sample into a 100 mL volumetric flask and dissolve in water. Dilute to volume with water and mix well.

Preparation of a Limit Stock Solution:

Pipette 5.0 mL of Calibration Standard Solution into a 100 mL volumetric flask and dilute to volume with water (5%)

Preparation of 0.05% Limit Test Solution:

Pipette 1.0mL of Limit Stock Solution into a 100 mL volumetric flask and dilute to volume with water.

Preparation of a System Suitability Solution:

Pipette 5.0 mL of stock standard solution into a 50 mL volumetric flask and add 2.0 mL of 10 volume peroxide. Dilute to volume with water and mix well. Fill a HPLC vial with the solution and heat for 30 minutes at 80ºC. When cooled inject this solution.

Analytical Solution Stability

Standard solutions are stable for 42 days when stored at ambient temperature.

Calculation of Amounts

Morphine sulfate and related substances are quantified by external standard and single point calibration. Related substances are quantified relative to Morphine sulfate with the use of relative response factors.

$$\text{Corrected Std Weight} = \frac{\text{weight taken (g)} \times \text{purity of standard}}{100}$$

$$\text{Morphine sulfate (\%w/v)} = \frac{\text{Corrected std weight} \times \text{Area Morphine sulfate in spl} \times 100 \times 100}{\text{Area Morphine Sulfate in std} \times 1}$$

$$\text{Rel Subs (\%w/v)} = \frac{\text{Corrected std weight x Area Rel Subs in spl x 100 x 100 x Factor}}{\text{Area Morphine Sulfate in std x 1}}$$

Results are calculated in %w/v, they can be converted to mg/mL using the following equation:

$$\text{Result (mg/mL)} = \frac{\text{Result (\%w/v) x 100}}{1000}$$

Expected retention times:

Component	**Retention time window/ Relative Retention Time (RRT)**	**Relative Response Factor**
Morphine sulfate	4.1- 4.5 minutes RRT 1.0	1.0
Impurity A (codeine)	7.4 – 8.0 minutes RRT 1.8	1.0
Impurity B (pseudomorphine)	3.2 – 3.5 minutes RRT 0.8	0.5
Impurity C	6.7 – 7.2 minutes RRT 1.6	0.4
Impurity E	4.4 – 4.7 minutes RRT 1.1	0.5
Impurity F	5.0 – 5.5 minutes RRT 1.2	1.0

Example chromatograms:

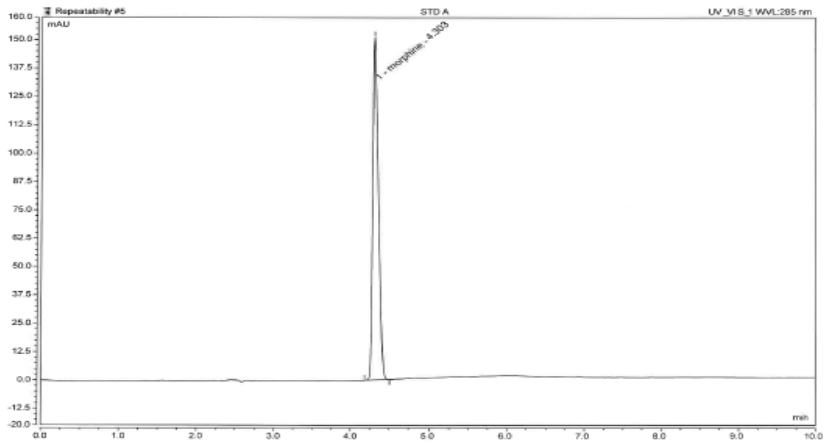


Figure P.5.2.1 – Chromatogram of a typical injection of calibration standard solution

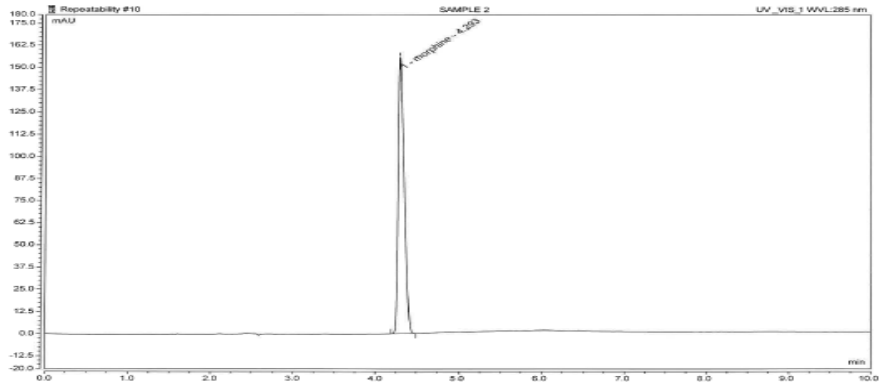


Figure P.5.2.2 – Chromatogram of a typical injection of test sample solution

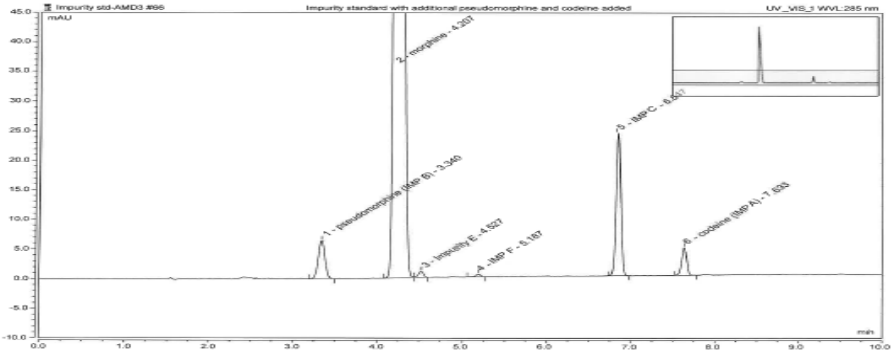


Figure P.5.2.3 – Chromatogram of an injection of morphine sulfate spiked with known impurities (baseline zoomed)

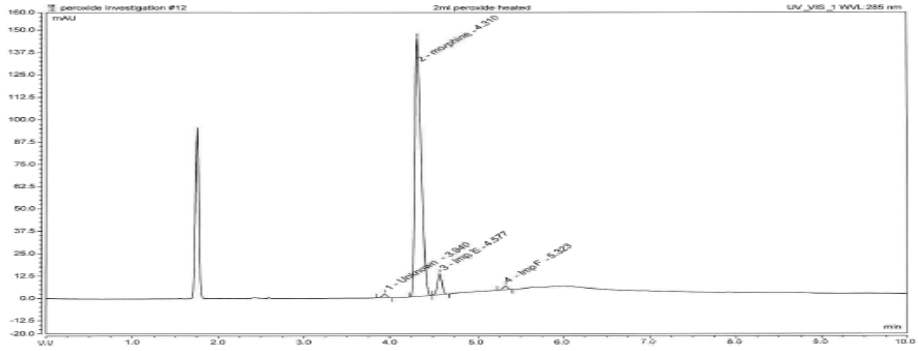


Figure P.5.2.4 – Chromatogram of an injection of the system suitability solution demonstrating resolution between morphine sulfate and Impurity B (pseudomorphine)

P.5.3 Validation of Analytical Procedures

The validation of analytical procedures is not required as they are taken from the European Pharmacopeia and British Pharmacopeia, if not stated otherwise below.

Assay of Morphine sulfate and known/unknown related substances by HPLC-UV

Parameter/Assessment	**Acceptance criteria**	**Result**
Specificity	• The peak due Morphine sulfate must be free from interference • The minimum resolution between Morphine sulfate and any other peak must be >1.5. • Peak purity of Morphine sulfate in all unadulterated samples should be between 98.0 – 102.0 % of the standard. • The UV spectra of Morphine sulfate must be concurrent between sample and standard.	Specificity confirmed
Linearity (Samples of Morphine sulfate at 0.05-120%)	Correlation Co-efficient R^2 >99.9%	R^2 = 100.00
Accuracy (spiked samples 0.05, 0.1, 1.0, 80, 100 and 120%; 6 repeats)	Recovered amounts should be as below: At 0.05%, within 70.0 – 130.0% 0.1%, within 80.0 – 120.0% At 1.0% within 90.0 – 110.0% At 80,100, 120% - within 98.0-102.0%	Accuracy confirmed for Morphine sulfate
Precision (repeatability) c) 6 replicates tested in duplicate, d) 10 repeats of same sample	c) %RSD ≤2.0 d) %RSD ≤1.0	c) 0.4%RSD d) 0.3%RSD
Limit of Detection of Morphine sulfate	S:N of approx. 10	0.025%, S:N 5.8
Limit of Quantification of Morphine sulfate	S:N of approx. 3	0.05%, S:N 10.5

Intermediate precision is not performed at this stage of the application.

P.5.3.1 Validation of the Test for Bioburden

Not required at this stage of the application

P.5.3.2 Validation of the Test for Sterility

The validation report has been included as Attachment 7.

P.5.3.3 Validation of the Test for Bacterial Endotoxins

The validation report has been included as Attachment 8.

P.5.4 Batch Analysis

The below batch is representative of a batch intended for use in the proposed clinical trial.

Test	**Batch number**	200217X
	Date of Manufacture	17Feb2020
	Batch size	2.5L (710 units sub batch)
	Acceptance Criteria	**Result**
Examination	A clear, colourless to pale yellow solution free from particulate contamination	Complies
pH	2.5 – 6.5	4.6
Identification of Morphine sulfate	1. Retention time comparison with a reference standard 2. UV Spectral Comparison with a reference standard	Complies Complies
Assay of Morphine sulfate	9.5 – 10.5mg/mL	10.1mg/mL
Codeine (Impurity A)	Not greater than 0.5%wrt API	0.05%wrt API
Any other single Known Related Substance	Not greater than 0.2% wrt API	Complies
Any other single Unknown Related Substance	Not greater than 0.2% wrt API	Complies
Total Known/Unknown Related Substances (%wrt API)	Not greater than 2.0% wrt API	Complies

Sterility Test	Pass	Pass
BET	<17.0 EU/mg	TBC
Sub-visible particle count	10µm ≤6000/container 25µm ≤600/container	28.5 0.7

P.7 Container Closure System

Primary Packaging

2ml Type 1 Fiolax clear Form D glass ampoules according to Ph. Eur. 3.2.1.

P.8 Stability

Storage Conditions:

Store in a dry place. Protect from light.

Shelf-life:

Based on historical data of existing morphine products an initial 12 months expiry is set for morphine 10mg/mL in 2mL glass ampoules containing 1mL with a rolling program to extend the shelf-life to 24 months from data available via an ongoing stability study plan (see 'Shelf-life Extension Program' below).

The preparation is to be used immediately after opening so no in-use stability data will be presented.

Samples from one batch of ampoules will be included in a supporting ongoing stability study program with analysis performed as described below. Data from this study will be reviewed at each time point to verify the predicted shelf life set at 24 months.

Stability control

The stability study protocol has been designed to provide assurance of ongoing stability:

Product Code	MOR19S	**Batch number**	200217X	**DOM**	17 Feb 2020
Product Name	Morphine sulphate injection				
Strength	10mg/mL		**Pack size**	1mL in 2mL ampoule	
Aim of Study					
Development batch to perform stability study in support of Packman clinical Trial C013					
Duration of Stability Study	18M				
Timepoints required	0,1,2,3,6,9,12,18,24M				
Storage Condition(s)	25°C/60%RH, 30°C/60%RH, 40°C/75%RH				

Testing Requirements:

Test	Description
(a)	Examination
(b)	pH
(c)	Assay and Related Substances
(d)	Sterility
(e)	Particle Counts
(f)	Bacterial Endotoxins

Timepoints No. of samples required (tests in brackets)

	T=0	1M	2M	3M	6M	9M	12M	18M	24M
5°C	97 (a – f)								
25°C				12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)	82 (a-e)
30°C				12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)		
40°C		12 (a–c)	12 (a–c)	12 (a–c)	12 (a–c)				

Shelf-life Extension Program

The initial 12 months stability may be extended during the Clinical Trial based on the results of the stability study performed on a test batch. In the extension, extrapolation will be used requiring real-time data of ketamine assay and degradation products before an expiry is set as follows:

Real-time stability data available	Proposed shelf-life
3 months accelerated (40°C/75%RH)	12 months
12 months at ambient	24months

The specification used will be the same as the Release analysis. Shelf-life will not be extended if the trend analysis performed according to ICH Q1E shows that the specification at the end of shelf-life is not met.

Stability results available at the time of submission are included in Attachment 9.

2.1.A Appendices

2.1.A.1 Facilities and Equipment

Role: Development and manufacture of ampoules, clinicals trials labelling, packaging, final QP release and storage/distribution

Calderdale and Huddersfield NHS Foundation Trust trading as Huddersfield Pharmacy Specials (HPS)

Manufacturing site: Acre Mills, Gate 2, School Street West, Lindley, Huddersfield, HD3 3ET, UK

MIA(IMP) Authorisation: MIA(IMP) 19055

2.1.A.2 Adventitious Agents Safety Evaluation

All materials used in the manufacture are assessed for compliance against TSE/BSE regulations during the supplier assessment by the respective manufacturers. The following TSE-free statements have been included as attachments to this dossier:

- Attachment 4: TSE-free statement for sodium chloride
- Attachment 10: TSE-free statement for disodium edetate
- Attachment 11: TSE-free statement for ketamine hydrochloride
- Attachment 12: TSE-free statement for morphine sulphate

2.1.A.3 Novel excipients

Not applicable.

2.1.A.4 Solvents for Reconstitution and Diluents

Not applicable.

2.1.A.5 Labelling

Secondary packaging label: Packs

PACKMaN
Pack Number: *pre-printed number as per randomisation list*

3 x 1mL ampoules containing either:
Ketamine 15mg/ml solution for injection or
Morphine 10mg/ml solution for injection

Directions for use: To be administered via the intravenous or intraosseous route as directed in the clinical trial protocol.

Storage Conditions: Store in a dry place. Protect from light.

Batch number: *pre-printed information assigned at manufacture*
Expiry Date: *dd/mmm/yyyy (assigned at manufacture)*

For emergency unblinding contact the regional ambulance control centre:

Yorkshire Ambulance Service: TBC.

West Midlands Ambulance Service: TBC.

Contact: Dr Michael Smyth, The University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL. Telephone: 02476 150478 (Warwick Clinical Trials Unit).

FOR CLINICAL TRIAL USE ONLY EudraCT No.: 2020-000154-10

Notes:

- Labels will be white with black text

Primary packaging label: ketamine and morphine ampoules

PACKMaN **Pack No**.: *pre-printed*
Ketamine 15mg/mL or Morphine 10mg/mL
intravenous or intraosseous injection

BN: *pre-printed information assigned at manufacture*

The University of Warwick

Notes:

- Labels will be white with black text

Rear of all IMP packs:

Inclusion criteria	Exclusion criteria
• Age ≥16 • Patient reports a pain score ≥7/10 on a 0-10 NRS following acute traumatic injury • Intravenous or intraosseous access obtained • Determined by a paramedic to require IV morphine or equivalent	• Known or suspected pregnancy • Unable to articulate severity of pain using the 0-10 NRS • Lack of capacity due to a reason other than pain • Ketamine or opioid analgesia prior to randomisation • Contraindication to either ketamine or morphine as per the SmPC • Patient declines participation • Known prisoner

2.1.A.6 Attachments

Attachment 1: MIA(IMP) for Calderdale and Huddersfield NHS Foundation Trust trading as Huddersfield Pharmacy Specials (HPS)

Attachment 2: Certificate of Suitability for ketamine hydrochloride

Attachment 3: Certificate of Suitability for morphine sulfate

Attachment 4: TSE-free statement for sodium chloride

Attachment 5: Sterility testing method validation report for ketamine hydrochloride injection 15mg in 1ml

Attachment 6: LAL validation report for ketamine hydrochloride injection 15mg in 1ml

Attachment 7: Sterility testing method validation report for morphine sulfate injection 10mg in 1ml

Attachment 8: LAL validation report for morphine sulfate injection 10mg in 1ml

Attachment 9: IMP stability test protocols and results (0, 3, 6, 9, 12M)

Attachment 10: TSE-free statement for disodium edetate

Attachment 11: TSE-free statement for ketamine hydrochloride

Attachment 12: TSE-free statement for morphine sulphate

Version Control

Version	Date	Comments
1.0	29 July 2020	New document.
1.1	16 Oct 2020	P.8 Stability (for both products): - Storage conditions amended to remove the 25°C restriction. 2.1.A.5 Labelling: - IO route of administration added to primary and secondary labels - Main contact details amended on the secondary label - Storage conditions amended on the secondary label - Emergency unblinding details amended on the secondary label - Label for rear of all packs: inclusion and exclusion criteria added Attachments: - Attachment 9: Stability results updated to include T6.
2.0	15 Mar 2021	P.1 Description and Composition (for both products): - Correction of typo in the table header: Amount is 1mL, not 5mL P.8 Stability (for both products): - Stability program timepoints amended to 18M and 24M (previously 14M and 18M) - Shelf-life extension program amended to propose a shelf-life of 24M based on 12M real time stability data Attachments: - Attachment 9: Stability results updated to include T12.

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 Version: 18

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) 19055

2. Name of Authorisation Holder

CALDERDALE AND HUDDERSFIELD NHS FOUNDATION TRUST

3. Trading Style

HUDDERSFIELD PHARMACY SPECIALS (HPS)

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:
431097	CALDERDALE AND HUDDERSFIELD NHS FOUNDATION TRUST	GATE 2 ACRE MILL, SCHOOL STREET WEST, HUDDERSFIELD, HD3 3ET, UNITED KINGDOM

5. Legally registered address of Authorisation Holder

GATE 2 ACRE MILL, SCHOOL STREET WEST, HUDDERSFIELD, HD3 3ET, UNITED KINGDOM

6. Scope of authorisation and dosage forms

See Annex 2

7. Legal basis of authorisation

See Section 1B of authorisation.

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 Version: 18

8. Name of responsible officer of the competent authority of the member state granting the manufacturing authorisation

Olumuyiwa Abimbola

SECTION 1A (continued)

9. Date 24/06/2020

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)

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 Version: 18

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.

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 Version: 18

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.

---

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) 19055 Version: 18

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
12/12/2005	Initial application
25/10/2006	Add two Qualified Persons Ms J L New and Mr J M Allen
21/02/2007	Internal Variation to amend errors on licence.
10/06/2008	Variation to add an additional site at Acre Mills and eight contract laboratories.
11/07/2008	Internal variation to correct errors.
23/09/2008	Variation to (1) Remove Mr John Harwood from Licence (2) Add Mr Don Wallace as LH contact (3) Add Mr Don Wallace as PM (4) Replace Mr Don Wallace with Mr J M Allen as QC (5) Add Mr Don Wallace as SC on sites 431097 & 11706. (6) Changes effective 08/09/2008.
26/10/2008	Update licence to EUDRA GMP format.
28/08/2009	Variation to remove Mr D Wallace as LH contact, QP and PM for sites: 431097 & 11706, and replace with Dr S.A.Langford. Remove Mr M Allen as QC and replace with Dr N.C. Crab. Remove site 20407 as requested by M.I.
23/07/2010	Variation: 1.Delete site 11706. 2. Site 431097 Remove Dr N Crabb as QC and replace him with Mr A Myers and update site activities.
08/10/2010	Variation to add site: 11706
05/07/2011	Variation to edit site 431097
03/06/2013	Variation to remove site 11706.
22/08/2013	Variation:1. Site 431097 delete Other Biologicals and Pressurised preparations.
30/08/2013	Internal variation to correct errors
29/10/2015	Variation: Add Ms Jodi New as PM (Site 431097)
21/11/2016	Variation: to add Roger Brookes as Head of Production and to remove Jodi New and Stephen Langford. Site no 431097

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 Version: 18

13/05/2019	Variation to add Primary packing activities. Change of trading style. Remove sites 4571, 9776. Add sites 16988769 and 92250 as contract laboratories
24/06/2020	Variation to: -Add Export to site 431097. -Add contract lab site 336740.

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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:	CALDERDALE AND HUDDERSFIELD NHS FOUNDATION TRUST
ADDRESS:	GATE 2 ACRE MILL, SCHOOL STREET WEST, HUDDERSFIELD, HD3 3ET, UNITED KINGDOM
MHRA SITE NUMBER:	431097

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

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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	Not Authorised
	1.1.1.3 Semi-solids	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

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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	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	Not Authorised
1.1.3	***Batch certification***	Authorised

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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	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 Special Requirements: Other Over encapsulation	Authorised
	1.2.1.9 Pressurised preparations	Not Authorised
	1.2.1.10 Radionuclide generators	Not Authorised
	1.2.1.11 Semi-solids	Authorised
	1.2.1.12 Suppositories	Authorised
	1.2.1.13 Tablets	Not Authorised

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

	1.2.1.14 Transdermal patches	Not Authorised
	1.2.1.15 Other non-sterile medicinal products	Not Authorised
1.2.2	***Batch certification***	Authorised

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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	Not Authorised
	1.3.1.6 Human or animal extracted products	Not Authorised
	1.3.1.7 Tissue Engineered Products	Not Authorised
	1.3.1.8 Other biological medicinal products	Not 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

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

	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

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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 Heparin and insulin	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

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

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	Authorised
	1.5.1.6 Liquids for internal use	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	Authorised
	1.5.1.12 Suppositories	Authorised
	1.5.1.13 Tablets	Authorised

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

	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

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

1.6	**Quality control testing**	
	1.6.1 Microbiological: sterility	Authorised
	1.6.2 Microbiological: non-sterility	Authorised
	1.6.3 Chemical/Physical	Authorised
	1.6.4 Biological	Not Authorised

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations:

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 MHRA Site No: 431097 VERSION: 18

ANNEX 5/6 – SITE INFORMATION (continued)

Personnel

Person Number	Name	Personnel Type			
		QP	TQP	PM	QC
13897503	Mr Roger Brookes	No	No	Yes	No
2342688	Mr Andrew Myers	No	No	No	Yes
625285	Mr J M Allen	No	Yes	No	No

Key to Roles:

QP – Qualified Person
TQP – Transitional Qualified Person
PM – Production Manager/Supervisor
QC – Person responsible for Quality Control

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 VERSION: 18

ANNEX 4 – CONTRACT LABORATORIES

MHRA SITE NUMBER:	LABORATORY NAME:	ADDRESS:
5566	QUALITY CONTROL NORTH WEST	STEPPING HILL HOSPITAL, STOCKPORT, SK2 7JE, UNITED KINGDOM
30429	HONEYMAN LIMITED	HARMIRE ENTERPRISE PARK, BARNARD CASTLE, DL12 8BN, UNITED KINGDOM
91520	PHARMACEUTICAL CHEMISTRY AND MICROBIOLOGY LAB (LIVERPOOL)	PHARMACY PRACTICE UNIT, 70 PEMBROKE PLACE, LIVERPOOL, L69 3GF, UNITED KINGDOM
92250	ALS LABORATORIES (UK) LIMITED	2 BARTHOLOMEW'S WALK, CAMBRIDGESHIRE BUSINESS PARK, ELY, CB7 4ZE, UNITED KINGDOM
93666	JC ANALYTICAL LIMITED	FLORENCE ROAD INDUSTRIAL ESTATE, KELLY BRAY, CALLINGTON, PL17 8EX, UNITED KINGDOM
318192	STOCKTON QUALITY CONTROL LABORATORY	UNIVERSITY HOSPITAL OF NORTH TEES, HARDWICK ROAD, STOCKTON-ON-TEES, TS19 8PE, UNITED KINGDOM
336740	MELBOURN SCIENTIFIC LIMITED TA INTERTEK MELBOURN	SAXON WAY, MELBOURN, ROYSTON, SG8 6DN, UNITED KINGDOM
16988769	NORTHUMBRIA PHARMA	NETPARK, THOMAS WRIGHT WAY, SEDGEFIELD, STOCKTON-ON-TEES, TS21 3FD, UNITED KINGDOM

Medicines & Healthcare products Regulatory Agency

MHRA

MIA(IMP) NUMBER: MIA(IMP) 19055 VERSION: 18

ANNEX 9 – STORAGE SITES

MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
431097	CALDERDALE AND HUDDERSFIELD NHS FOUNDATION TRUST	GATE 2 ACRE MILL, SCHOOL STREET WEST, HUDDERSFIELD, HD3 3ET, UNITED KINGDOM

edqm
European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2005-281-Rev 00

Name of the substance:
KETAMINE HYDROCHLORIDE

Name of holder:
CU CHEMIE UETIKON GMBH
Raiffeisenstrasse 4
Germany-77933 Lahr

Site(s) of production:
CU CHEMIE UETIKON GMBH
Raiffeisenstrasse 4
Germany-77933 Lahr

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2005-281-REV 01

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production mentioned above, we certify that the quality of the substance is suitably controlled by the current version of the monograph **Ketamine hydrochloride** no. 1020 of the European Pharmacopoeia, current edition including supplements.

In the last steps of the synthesis acetone and ethyl acetate are used as solvents. Their residual content is limited by the test for loss on drying described in the monograph, with a limit of not more than 0.5%.

The substance is packed in double polyethylene bags placed in a polyethylene drum.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Address: 7, allée Kastner, CS 30026
F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

Certification of Substances Department

Certificate of suitability
No. R1-CEP 2001-239-Rev 06

Name of the substance:
MORPHINE SULFATE

Name of holder:
MACFARLAN SMITH LIMITED
10 Wheatfield Road
United Kingdom-EH11 2QA Edinburgh, Scotland

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2001-239-REV 05

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph **MORPHINE SULFATE** no. 1244 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

Any unspecified impurity detected by the test for related substances of the monograph is limited to not more than 0.10%.

– Test for residual solvents by gas chromatography (Annex 2)
Ethanol not more than 5000 ppm
Methanol not more than 3000 ppm

The re-test period of the substance is 5 years if stored in a polyethylene bag placed in either a polyethylene, aluminium or polypropylene container.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Failure to comply with these provisions will render this certificate void.

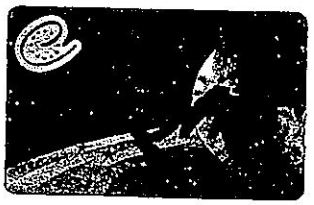
This certificate is renewed from **29 July 2007** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has two annexes, the first of 1 page and the second of 2 pages.

This certificate has:

lines.

On behalf of the
Director of EDQM



Strasbourg, 27 February 2017

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

MACFARLAN SMITH LIMITED, as holder of the certificate of suitability

R1-CEP 2001-239-Rev 06 for Morphine sulfate

hereby authorises Huddersfield Pharmacy Specials
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

For information only

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):

17 MARCH 2020

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Certification of Substances Department

Annex 1: Site(s) of production for R1-CEP 2001-239-Rev 06

Production of Morphine sulfate:
MACFARLAN SMITH LIMITED
10 Wheatfield Road
United Kingdom-EH11 2QA Edinburgh, Scotland

Residual Solvents

Internal Standard Stock Solution

Pipette 0.2ml of n-propanol into a 100ml volumetric flask and dilute to volume with purified water.

Calibration Stock Solution

Pipette 1ml of methanol, 1ml of ethanol, 1ml of acetone and 1ml of isopropanol into a 500ml volumetric flask containing about 450ml of purified water. Shake vigorously to dissolve. Dilute to volume with purified water.

Level 1 Calibration Solution

Pipette 20ml of Calibration Stock Solution and 20ml of Internal Standard Stock Solution into a 2000ml volumetric flask and dilute to volume with purified water. Transfer 10ml aliquots into suitable vials and crimp seal.

Level 2 Calibration Solution

Pipette 100ml of Calibration Stock Solution and 20ml of Internal Standard Stock Solution into a 2000ml volumetric flask and dilute to volume with purified water. Transfer 10ml aliquots into suitable vials and crimp seal.

Sample Internal Standard Solution

Pipette 20ml of Internal Standard Stock Solution into a 2000ml volumetric flask and dilute to volume with purified water.

Test Solution

Weigh accurately about 1g of sample into a suitable vial. Add 10ml of sample Internal Standard Solution and crimp seal. Ensure that the sample is dissolved before continuing. Prepare 2 such vials for each sample.

Headspace Autosampler Conditions

Sample temperature	:	70°C
Needle temperature	:	100°C
Transfer temperature	:	180°C
GC cycle time	:	15 minutes
Thermostatting time	:	15 minutes
Pressurisation time	:	2 minutes
Inject time	:	0.1 minutes
Withdrawal time	:	0.2 minutes

GC Conditions

Column	:	RTX-1701 (Crossbond 14% cyanopropylphenyl 86% dimethylpolysiloxane)
Column dimensions	:	60 metre length 0.53mm internal diameter 3.0 micron film thickness
Restrictor column	:	5m length 0.25mm internal diameter
Carrier gas	:	Helium
Pressure	:	30 psi
Oven temperature	:	50°C
Injection temperature	:	180°C
Detector	:	FID
Detector temperature	:	250°C

Procedure

Place a Level 1 Calibration, a Level 2 Calibration and 2 vials for each sample into the headspace autosampler carousel and start the autosampler.

Calculation

Calculate the ratio of component peak area to n-propanol area in each of the chromatograms. Plot a graph of ratio against concentration for both calibrations and obtain the equation for the straight line. From this equation the concentration of each component in the sample can be calculated.

TSE/BSE-Certificate

116224 Sodium chloride EMPROVE® EXPERT Ph Eur,BP,JP,USP

The note for guidance EMA/410/01 Rev. 3 of the EC considers the requirements of raw materials used for human and veterinary medicinal products. The document introduces risk assessment into the regulatory compliance process for products derived from TSE/BSE-relevant animal species.

We certify that this product is manufactured without the use of raw materials of animal or human origin.

Sodium chloride is synthetically produced.

During processing the product does not come in contact with animal material.

Therefore, the product does not fall under the scope of the above-mentioned guideline and is not concerned by the TSE/BSE issue.

Dr. Jörg Schröder
Quality Services

This document has been produced electronically and is valid without a signature.

Date: 03-Mar-2020

Merck KGaA, Darmstadt, Germany
Corporation with General Partners
Frankfurter Str. 250
64293 Darmstadt, Germany
Phone +49 6151 72-0

Sigma-Aldrich Corporation
A subsidiary of Merck KGaA, Darmstadt, Germany
3050 Spruce Street
St. Louis, MO 63103, USA
Phone +1 (800) 521-8956 +1 (314) 771-5765

EMD Millipore Corporation
A subsidiary of Merck KGaA, Darmstadt, Germany
400 Summit Drive
Burlington, MA 1803, USA
Phone +1 (781) 533-6000

NHS	Calderdale & Huddersfield NHS Foundation Trust Pharmacy Manufacturing Unit Acre Mill Site	HPS
Sterility Testing Validation Appendices	Appendix 7 Sterility Test Validation Report for Products	Revision: A

Sterility Testing -
Method Validation Report for

Ketamine Hydrochloride Injection 15mg in 1ml

Section 1 – Product Information

Product Details			
Syspro Title:	Ketamine Hydrochloride Injection	**Syspro Code:**	*KET01S*
Batch Size:	*1701*	Container (Inc. Syspro code)	*AC2 – 2ml Amp*
Fill Volume:	*1.2ml*	Closure (Inc. Syspro code)	*As Above*

Sterility Testing Details			
Where Tested:	*HPS*		
Type of product:	*Parenteral*	Dose:	*Single*

Raw Materials Used and Grouping of Products			
Syspro Code	Syspro Title	Amount	Antimicrobial (AM) or Solvent(Sol)
R411	KETMINE HYDROCHLORIDE	43.238g	NO
R250	Sodium Chloride	22.5g	NO

Are any other products covered by this validation:	*No*

If Yes, please state which products are covered and complete 'appendix 8' for each product:

Syspro Title	Syspro Code	Appendix 8 completed (✓)
N/A	N/A	N/A

NHS	Calderdale & Huddersfield NHS Foundation Trust Pharmacy Manufacturing Unit Acre Mill Site	HPS
Sterility Testing Validation Appendices	Appendix 7 Sterility Test Validation Report for Products	Revision: A

Section 2 – Sterility Method Information

Sample Details (as per appendix 4)			
No. of Containers:	*40*	Volume per Media:	*All content*
Sterility Testing Method			
Steritest EZ Device (please tick):	*Blue (mixed cellulose)*	If using red or green, give justification:	QC0328/08
Steritest EZ Adaptors (please tick):	*Ampoules / Collapsible bags*	If deviating from recommended adaptor, give justification:	F22/79
Fluid (please tick):	*Fluid A*	If not using standard diluent, give justification:	QC0330/12 , QC0329/12
No of washes (please tick):	*3 washes*	If using 5 washes, give justification below: 2 x 50ml then 1 X 100ml per canister	THS/196 TSB/103

Section 3 - Results

Batch 1		**Batch 2**		**Batch 3**	
BN:	*300218X*	BN:	*400218X*	BN:	*500218X*
Session No:	*STVAL2001*	Session No:	*STVAL2001*	Session No:	*STVAL2001*
A.brasiliensis	*G*	A.brasiliensis	*G*	A.brasiliensis	*G*
B.subtilis	*G*	B.subtilis	*G*	B.subtilis	*G*
C.albicans	*G*	C.albicans	*G*	C.albicans	*G*
C.sporogenes	*G*	C.sporogenes	*G*	C.sporogenes	*G*
P.aeruginosa	*G*	P.aeruginosa	*G*	P.aeruginosa	*G*
S.aureus	*G*	S.aureus	*G*	S.aureus	*G*
Batch Outcome:	*Pass*	Batch Outcome:	*Pass*	Batch Outcome:	*Pass*

Section 4 - Approval

Approval			
Validation approved by:	A.M (QC Manager or Deputy)	Date:	15 JUNE 2020

LAL Validation Form – KT method

Product Name	Ketamine Hydrochloride Injection 15mg in 1ml				
Product Code	KETAØ7L				
Client	Huddersfield				
ELC	700 EU/ml	MVD	700,000x	CALCULATION REF	Client's email

PRELIMINARY TESTING – 10 FOLD DILUTIONS					
Reagent Lots					
LYSATE	519-08-934-T	CSE	170	LRW	AE28251284
Dilution	Spike Recovery				
Neat	None.				
10x	None.				
100x	75%				
1000x	105%				
10000x	137%	100,000x 135%			
Analyst Ref	JMO	Pyros File	29/06/2020-JMO-A		

PRELIMINARY TESTING – 2FOLD DILUTIONS					
Reagent Lots					
LYSATE	519-08-934-T	CSE	170	LRW	AE28251284
Dilution	Spike Recovery				
10x	None.				
20x	8%				
40x	10%				
80x	24%				
160x 320x	46% 54%	640x 54% 1280x 63%			
Analyst Ref	IP	Pyros File	06/07/2020B		

VALIDATION TESTING								
Product Batch No.	Dilution Factor	Product Spike Recovery	Water Spike Recovery	Pyros File	Analyst Ref	Lysate Lot	CSE Lot	LRW Lot
300218X	1280x	63%	117%	06/07/2020B	IP	519-08-934-T	170	AE2825 1284
500218X	1280x	78%	123%	7/7/2020A	IP	519-08-934-T	170	AE285 1284
400218X	1280x	78%	123%	7/7/2020A	IP	519-08-934-T	170	AE285 1284

pH CHECK		
	pH	Analyst Ref
Product at 1280x dilution + lysate (1:1)	6.452	~~AMcmahon~~ 07/07/2020 AM (6) 201

Other Requirements	

V.3.1.1.

Quality Control North West

Title LAL Validation Form – KT Method

Issue Date: 9/12/14

Issued by: D. Rigg

QC Lab Manager: _____

NHS	Calderdale & Huddersfield NHS Foundation Trust Pharmacy Manufacturing Unit Acre Mill Site	HPS
Sterility Testing Validation Appendices	Appendix 7 Sterility Test Validation Report for Products	Revision: A

Sterility Testing -
Method Validation Report for

Morphine Sulphate Injection 10mg in 1ml

Section 1 – Product Information

Product Details			
Syspro Title:	*Morphine Sulphate Injection*	**Syspro Code:**	*MOR19S*
Batch Size:	*2.5L*	Container (Inc. Syspro code)	*AC2 – 2ml Amp*
Fill Volume:	*1.2ml*	Closure (Inc. Syspro code)	*As Above*

Sterility Testing Details			
Where Tested:	*HPS*		
Type of product:	*Parenteral*	Dose:	*Single*

Raw Materials Used and Grouping of Products

Syspro Code	Syspro Title	Amount	Antimicrobial (AM) or Solvent(Sol)
R171	Morphine Sulphate	25.0g	NO
R250	Sodium Chloride	22.5g	NO
R089	Disodium Edetate	2.5g	YES

Are any other products covered by this validation:	*No*

If Yes, please state which products are covered and complete 'appendix 8' for each product:

Syspro Title	Syspro Code	Appendix 8 completed (✓)
N/A	N/A	N/A

NHS	Calderdale & Huddersfield NHS Foundation Trust Pharmacy Manufacturing Unit Acre Mill Site	HPS
Sterility Testing Validation Appendices	Appendix 7 Sterility Test Validation Report for Products	Revision: A

Section 2 – Sterility Method Information

Sample Details (as per appendix 4)			
No. of Containers:	*40*	Volume per Media:	*All content*
Sterility Testing Method			
Steritest EZ Device (please tick):	*Blue (mixed cellulose)*	If using red or green, give justification:	QC0328/08
Steritest EZ Adaptors (please tick):	*Ampoules / Collapsible bags*	If deviating from recommended adaptor, give justification:	F22/79
Fluid (please tick):	*Fluid A*	If not using standard diluent, give justification:	QC0330/12 , QC0329/12
No of washes (please tick):	*3 washes*	If using 5 washes, give justification below: 2 x 50ml then 1 X 100ml per canister	THS/196 TSB/103

Section 3 - Results

Batch 1		Batch 2		Batch 3	
BN:	*200217X*	BN:	*300217X*	BN:	*400217X*
Session No:	*STVAL2001*	Session No:	*STVAL2001*	Session No:	*STVAL2001*
A.brasiliensis	*G*	A.brasiliensis	*G*	A.brasiliensis	*G*
B.subtilis	*G*	B.subtilis	*G*	B.subtilis	★
C.albicans	*G*	C.albicans	*G*	C.albicans	*G*
C.sporogenes	*G*	C.sporogenes	*G*	C.sporogenes	*G*
P.aeruginosa	*G*	P.aeruginosa	*G*	P.aeruginosa	*G*
S.aureus	*G*	S.aureus	*G*	S.aureus	*G*
Batch Outcome:	*Pass*	Batch Outcome:	*Pass*	Batch Outcome:	*Pass*

Section 4 – Approval

★ **See OOS 2020/19**

Sheet 1 of 2

Approval			
Validation approved by:	Jutell (QC Manager or Deputy)	Date:	24 Jul 2020

NHS	Calderdale & Huddersfield NHS Foundation Trust Pharmacy Manufacturing Unit Acre Mill Site	HPS
Sterility Testing Validation Appendices	Appendix 7 Sterility Test Validation Report for Products	Revision: A

Sterility Testing -
Method Validation Report for

Morphine Sulphate Injection 10mg in 1ml

Section 1 – Product Information

Product Details			
Syspro Title:	*Morphine Sulphate Injection*	**Syspro Code:**	*MOR19S*
Batch Size:	*2.5L*	Container (Inc. Syspro code)	*AC2 – 2ml Amp*
Fill Volume:	*1.2ml*	Closure (Inc. Syspro code)	*As Above*

Sterility Testing Details			
Where Tested:	*HPS*		
Type of product:	*Parenteral*	Dose:	*Single*

Raw Materials Used and Grouping of Products

Syspro Code	Syspro Title	Amount	Antimicrobial (AM) or Solvent(Sol)
R171	Morphine Sulphate	25.0g	NO
R250	Sodium Chloride	22.5g	NO
R089	Disodium Edetate	2.5g	YES

Are any other products covered by this validation:	*No*

If Yes, please state which products are covered and complete 'appendix 8' for each product:

Syspro Title	Syspro Code	Appendix 8 completed (✓)
N/A	N/A	N/A

NHS	Calderdale & Huddersfield NHS Foundation Trust Pharmacy Manufacturing Unit Acre Mill Site	HPS
Sterility Testing Validation Appendices	Appendix 7 Sterility Test Validation Report for Products	Revision: A

Section 2 – Sterility Method Information

Sample Details (as per appendix 4)			
No. of Containers:	*40*	Volume per Media:	*All content*

Sterility Testing Method			
Steritest EZ Device (please tick):	*Blue (mixed cellulose)*	If using red or green, give justification:	QC0328/06
Steritest EZ Adaptors (please tick):	*Ampoules / Collapsible bags*	If deviating from recommended adaptor, give justification:	F22/82
Fluid (please tick):	*Fluid A*	If not using standard diluent, give justification:	QC0330/14, QC0329/14
No of washes (please tick):	*3 washes*	If using 5 washes, give justification below: 2 x 50ml then 1 X 100ml per canister	THS/199 TSB/105

Section 3 - Results

Batch 1		Batch 2		Batch 3	
BN:	*400217X*	BN:		BN	
Session No:	*STVAL2002*	Session No:		Session No:	
A.brasiliensis		A.brasiliensis		A.brasiliensis	
B.subtilis	*G*	B.subtilis		B.subtilis	
C.albicans		C.albicans		C.albicans	
C.sporogenes		C.sporogenes		C.sporogenes	
P.aeruginosa		P.aeruginosa		P.aeruginosa	
S.aureus		S.aureus		S.aureus	
Batch Outcome:	*Pass*	Batch Outcome:		Batch Outcome:	

Section 4 – Approval Sheet 2 of 2

Approval			
Validation approved by:	(QC Manager or Deputy)	Date:	24 Jul 2020

LAL Validation Form – KT method

Product Name	Morphine Sulphate Injection 10mg in 1ml				
Product Code	MORP27L				
Client	Huddersfield				
ELC	700 EU/mL	MVD	700,000 x	CALCULATION REF	Client's email

PRELIMINARY TESTING – 10 FOLD DILUTIONS					
Reagent Lots					
LYSATE	519-08-934-T	CSE	170	LRW	AE28251284
Dilution	Spike Recovery				
Neat	None				
10x	14%				
100x	134%				
1000x	150%				
10000x	164% | 100,000X 155%				
Analyst Ref	JMO	Pyros File		29/06/2020 – JMO – A	

PRELIMINARY TESTING – 2FOLD DILUTIONS					
Reagent Lots					
LYSATE	519-08-934-T	CSE	170	LRW	AE28251284
Dilution	Spike Recovery				
10x	7%				
20x	35%				
40x	82%				
80x	103%				
.....x					
Analyst Ref	IP	Pyros File		06/07/2020A	

VALIDATION TESTING								
Product Batch No.	Dilution Factor	Product Spike Recovery	Water Spike Recovery	Pyros File	Analyst Ref	Lysate Lot	CSE Lot	LRW Lot
200217X 200212 IP 6/7/2020	80 x	103%	147%	06/07/2020 A	IP	519-08-934 -T	170	AE2825 1284
300217X	80 x	67%	117%	06/07/2020 B	IP	519-08-934 -T	170	AE2825 1284
400217X	80 x	66%	117%	06/07/2020 B	IP	519-08-934 -T	170	AE2825 1284

pH CHECK		
	pH	Analyst Ref
Product at 80 x dilution + lysate (1:1)	6.421	~~AM~~ 07/07/2020 AM (6)201

Other Requirements	

V.310

Quality Control North West

Title LAL Validation Form – KT Method

Issue Date: 9/12/14

Issued by: D. Rigge

QC Lab Manager:

Calderdale and Huddersfield NHS
NHS Foundation Trust

Product Code	KET01S	Batch number	300218X	DOM	18-Feb-20
Product Name	Ketamine Injection				
Strength	15mg/mL		Pack size	1mL in 2mL ampoule	
Stability Protocol Reference	SLJ_KET01S_001_results				
Duration of Stability Study	24M				
Timepoints required	0,3,6,9,12,18,24M				
Storage Condition(s)	25°C/60%RH				

Test	Specification		Timepoint/pull date									
			T=0		1M	2M	3M	6M	9M	12M	15M	18M	24M
			1st	Random									
Examination	Complies		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies			
pH	Record		4.51	4.58			4.70	4.77	4.77	4.85			
Identification of Ketamine	1. Complies		Complies	Complies									
	2. Complies		Complies	Complies									
Ketamine (15mg/mL)	14.25-15.75mg/m L 95.0-105.0% nominal		15.55	15.47	14.94	14.78	15.25	15.46	15.44	15.07			
Known/unkown related substances (%wrt API)	NGT 0.5% wrt API ,with not more than one greater than 0.25%	RT 18.0	ND	ND	ND	ND	ND	ND	ND	0.04			
		RT 26.2	ND	ND	ND	ND	ND	ND	ND	0.07			
		RT 7.6	0.16	0.10			ND	ND	ND	0.03			
		Imp A	0.42	0.41	0.40	0.42	0.32	0.20	0.41	0.4			
Total known/unkown related substances (%wrt API)	NGT 1.0 %		0.58	0.51	0.40	0.42	0.32	0.20	0.41	0.54			
Sterility	Complies												
Particle Counts	10µm ≤ 6000/container		9.1										
	25µm ≤ 600/container		0.4										

Method reference KET01S **version** I

ND = None detected
NT= Not Tested

PACKMaN IMPD: Attachment 9

Calderdale and Huddersfield NHS
NHS Foundation Trust

Product Code	KET01S	Batch number	300218X	DOM	18-Feb-20
Product Name	Ketamine Injection				
Strength	15mg/mL		Pack size	1mL in 2mL ampoule	
Stability Protocol Reference	SLJ_KET01S_001_results				
Duration of Stability Study	24M				
Timepoints required	3M, 6M, 9M, 12M				
Storage Condition(s)	30°C/65%RH				

Test	Specification		Timepoint/pull date					
			T=0		3M	6M	9M	12M
			1st	Random				
Examination	Complies		Complies	Complies	Complies	Complies	Complies	Complies
pH	Record		4.51	4.58	4.71	4.81	4.82	4.85
Identification of Ketamine	1. Complies		Complies	Complies				
	2. Complies		Complies	Complies				
Ketamine (15mg/mL)	14.25-15.75mg/m L 95.0-105.0% nominal		15.55	15.47	15.39	15.41	15.39	15.16
Known/unkown related substances (%wrt API)	NGT 0.5% wrt API ,with not more than one greater than 0.25%	RT 18.0	ND	ND	ND	ND	ND	0.05
		RT 26.2	ND	ND	ND	ND	ND	0.07
		RT 7.6	0.16	0.1	ND	ND	ND	ND
		Imp A	0.42	0.41	0.32	0.21	0.42	0.40
Total known/unkown related substances (%wrt API)	NGT 1.0 %		0.58	0.51	0.32	0.21	0.42	0.52
Sterility	Complies							
Particle Counts	10µm ≤ 6000/container		9.1					
	25µm ≤ 600/container		0.4					

Method reference KET01S **version** I

ND = None detected

NT= Not Tested

PACKMaN IMPD: Attachment 9

Calderdale and Huddersfield NHS
NHS Foundation Trust

Product Code	**KET01S**	**Batch number**	**300218X**	**DOM**	**18-Feb-20**
Product Name	**Ketamine Injection**				
Strength	**15mg/mL**		**Pack size**	**1mL in 2mL ampoule**	
Stability Protocol Reference	**SLJ_KET01S_001_results**				
Duration of Stability Study	**24M**				
Timepoints required	**1M, 2M, 3M, 6M**				
Storage Condition(s)	**40°C/75%RH**				

		Timepoint/pull date					
Test	**Specification**	**T=0**		**1M**	**2M**	**3M**	**6M**
		1st	**Random**				
Examination	Complies	Complies	Complies	Complies	Complies	Complies	Complies
pH	Record	4.51	4.58	4.81	4.94	4.78	4.86
Identification of Ketamine	1. Complies 2. Complies	Complies	Complies				
Ketamine (15mg/mL)	14.25-15.75mg/m L 95.0-105.0% nominal	15.55	15.47	15.11	14.53	15.32	15.26
Known/unkown related substances (%wrt API)	NGT 0.5% wrt API ,with not more than one greater than 0.25%	RT 7.6	0.10			ND	ND
		Imp A	0.41	0.41	0.43	0.33	0.22
Total known/unkown related substances (%wrt API)	NGT 1.0 %	0.58	0.51	0.41	0.43	0.33	0.22
Sterility	Complies						
Particle Counts	10µm ≤ 6000/container	9.1					
	25µm ≤ 600/container	0.4					

Method reference KET01S **version** I

ND = None detected

NT= Not Tested

PACKMaN IMPD: Attachment 9

Calderdale and Huddersfield NHS
NHS Foundation Trust

Product Code	MOR19S	Batch number	200217X	DOM	17-Feb-20
Product Name	Morphine Sulphate Injection				
Strength	10mg/mL		Pack size	1mL in 2mL ampoule	
Stability Protocol Reference	SLJ_MOR19S_001_results				
Duration of Stability Study	24M				
Timepoints required	0,3,6,9,12,18,24M				
Storage Condition(s)	25°C/60%RH				

Test	Specification		Timepoint/pull date T=0 1st Filled	T=0 Random	3M	6M	9M	12M	15M	18M	24M
Examination	Complies		Complies	Complies	Complies	Complies	Complies	Complies			
pH	Record		4.58	4.63	4.66	4.54	4.64	4.88			
Identification of Morphine Sulphate	1. Complies 2. Complies		Complies	Complies							
Morphine Sulphate (10mg/mL)	**Release**: 9.5-10.5mg/mL (95.0-105.0% nominal) **Over Shelf Life:** 9.25-10.75mg/mL (92.5 - 107.5%)		10.13	10.12	10.15	10.09	9.94	10.12			
Known/unkown related substances (%wrt API)	NGT 0.5% wrt API , with not more than one greater than 0.2%	**IMP A**	0.05	0.03	ND	0.03	0.04	0.07			
		IMP B	ND	ND	ND	ND	0.02	ND			
		IMP C	0.07	0.09	0.03	0.03	ND	0.01			
		IMP E	0.05	0.04	0.02	0.01	0.01	ND			
		IMP F	0.04	ND	ND	ND	ND	ND			
		Unknown @ RT 3.9	0.04	0.03	ND	0.01	ND	ND			
		Unknown @ RT 5.0	0.06	ND	ND	0.00	ND	ND			
		Unknown @ RT 4.8	ND	ND	ND	ND	0.01	0.02			
		Unknown @ RT 6.7	ND	ND	ND	ND	0.08	ND			
Total known/unkown related substances (%wrt API)	NGT 2.0 %		0.31	0.19	0.05	0.08	0.16	0.10	0.00	0.00	0.00
Sterility	Complies		Complies								
Particle Counts	10µm ≤6000/container		28.5								
	25µm ≤600/container		0.7								
Bacterial Endotoxins	17 EU/mg										

Method reference MOR19S **version** I

ND = None detected

NT= Not Tested

PACKMaN IMPD: Attachment 9

Calderdale and Huddersfield NHS
NHS Foundation Trust

Product Code	MOR19S	Batch number	200217X	DOM	17-Feb-20
Product Name	Morphine Sulphate Injection				
Strength	10mg/mL		Pack size	1mL in 2mL ampoule	
Stability Protocol Reference	SLJ_MOR19S_001_results				
Duration of Stability Study	24M				
Timepoints required	3M, 6M, 9M, 12M				
Storage Condition(s)	30°C/65%RH				

Test	Specification		Timepoint/pull date					
			T=0		3M	6M	9M	12M
			1st Filled	Random				
Examination	Complies		Complies	Complies	Complies	Complies	Complies	Complies
pH	Record		4.58	4.63	4.63	4.68	4.69	4.71
Identification of Morphine Sulphate	1. Complies 2. Complies		Complies	Complies				
Morphine Sulphate (10mg/mL)	**Release**: 9.5-10.5mg/mL (95.0-105.0% nominal) **Over Shelf Life:** 9.25-10.75mg/mL (92.5 - 107.5%)		10.13	10.12	10.12	10.09	9.99	10.08
Known/unkown related substances (%wrt API)	NGT 0.5% wrt API , with not more than one greater than 0.2%	**IMP A**	0.05	0.03	ND	0.03	0.04	0.08
		IMP B	ND	ND	ND	0.02	0.02	ND
		IMP C	0.07	0.09	0.03	0.03	ND	0.01
		IMP E	0.05	0.04	ND	0.01	0.02	ND
		IMP F	0.04	ND	ND	ND	ND	ND
		Unknown @ RT 3.9	0.04	0.03	ND	0.01	ND	ND
		Unknown @ RT 5.0	0.06	ND	ND	0.00	ND	ND
		Unknown @ RT 4.8	ND	ND	ND	ND	0.03	ND
		Unknown @ RT 6.7	ND	ND	ND	0.00	0.08	ND
Total known/unkown related substances (%wrt API)	NGT 2.0 %		0.31	0.19	0.03	0.09	0.19	0.09
Sterility	Complies		Complies					
Particle Counts	10µm ≤ 6000/container		28.5					
	25µm ≤ 600/container		0.7					
Bacterial Endotoxins	17 EU/mg							

Method reference MOR19S **version** I

ND = None detected

NT= Not Tested

PACKMaN IMPD: Attachment 9

Calderdale and Huddersfield NHS
NHS Foundation Trust

Product Code	**MOR19S**	**Batch number**	**200217X**	**17-Feb-20**
Product Name	**Morphine Sulphate Injection**			
Strength	**10mg/mL**		**Pack size**	**2mL**
Stability Protocol Reference	**SLJ_MOR19S_001_results**			
Duration of Stability Study	**24M**			
Timepoints required	**1M, 2M, 3M, 6M**			
Storage Condition(s)	**40°C/75%RH**			

			Timepoint/pull date					
Test	**Specification**		**T=0**		**1M**	**2M**	**3M**	**6M**
			1st Filled	**Random**				
Examination	Complies		Complies	Complies	Complies	Complies	Complies	Complies
pH	Record		4.58	4.63	4.73	4.68	4.65	4.68
Identification of Morphine Sulphate	1. Complies 2. Complies		Complies	Complies				
Morphine Sulphate (10mg/mL)	**Release**: 9.5-10.5mg/mL (95.0-105.0% nominal) **Over Shelf Life:** 9.25-10.75mg/mL (92.5 - 107.5%)		10.13	10.12	10.05	10.28	10.14	10.06
Known/unkown related substances (%wrt API)	NGT 0.5% wrt API , with not more than one greater than 0.2%	**IMP A**	0.05	0.03	0.04	0.09	ND	0.03
		IMP B	ND	ND	ND	0.01	0.02	0.03
		IMP C	0.07	0.09	0.03	ND	0.03	0.03
		IMP E	0.05	0.04	0.01	0.02	0.01	0.01
		IMP F	0.04	ND	ND	ND	ND	ND
		Unknown @ RT 3.9	0.04	0.03	0.05	0.04	ND	0.01
		Unknown @ RT 5.0	0.06	ND	ND	ND	ND	0.00
		Unknown @ RT 8.0	ND	ND	ND	0.05	ND	ND
Total known/unkown related substances (%wrt API)	NGT 2.0 %		0.31	0.19	0.13	0.21	0.06	0.12
Sterility	Complies							
Particle Counts	10µm ≤ 6000/container		28.5					
	25µm ≤ 600/container		0.7					
Bacterial Endotoxins	17 EU/mg							

Method reference MOR19S **version** I

ND = None detected

NT= Not Tested

PACKMaN IMPD: Attachment 9

AkzoNobel
Chelates and Micronutrients

Endorsement Letter

Deventer, October 27, 2017

TO WHOM IT MAY CONCERN

Herewith we confirm that in the production of

all DISSOLVINE® products

produced by

Akzo Nobel Functional Chemicals

no material of animal origin has been used during the whole production process. This also includes materials used as reagents (e.g. bovine serum albumin, enzymes, culture media incl. those to prepare working cell banks or new master cell banks)"

Also the plant equipment used does not come in contact with any material of animal origin.

Based on these data we declare that all Dissolvine products are **TSE** (including **BSE**) free.

Yours sincerely,

J. Feddema
Technical Service
Chelates and Micronutrients
Ethylene and Sulfur Derivatives

Akzo Nobel Functional Chemicals B.V.
P.O. Box 10
7400 AA Deventer
the Netherlands

Arena Pharmaceuticals Ltd
Unit 14, Apollo Office Court
Radclive Road
Gawcott
Buckingham
MK18 4DF

MHRA Registration Ref: API42376

Reed 13 May 2020

CU Chemie Uetikon GmbH
Raiffeisenstr. 4
D-77933 Lahr
Germany

TO WHOM IT MAY CONCERN

Lahr, August 21, 2018

CONFIRMATION
of Material Origin for BSE/TSE Risk Evaluation

We hereby confirm, that our API

Ketamine Hydrochloride (product code: K1350)

is produced by chemical synthesis. It is not derived from any animal origin. It is therefore out of the scope of the current Ph. Eur. monograph <5.2.8> "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

There are validated cleaning procedures in place to avoid cross contamination. These procedures also minimize any risk of potential carry over of residues of animal origin materials which came into contact with the equipment before using it for the manufacture of the above mentioned material.

Sincerely,

CU Chemie Uetikon GmbH

i.A. Alina Wetternek
Regulatory Affairs Specialist

Johnson Matthey
Inspiring science, enhancing life

Macfarlan Smith Limited
Wheatfield Road
Edinburgh
EH11 2QA

T +44 (0) 131 337 2434
F +44 (0) 131 337 4436

LETTER OF DECLARATION OF MANUFACTURE REGARDING THE USE OF MATERIAL OF HUMAN OR ANIMAL ORIGIN INCLUDING SUBSTANCES AT RISK OF TRANSMITTING AGENTS OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

Macfarlan Smith Limited hereby confirms compliance with the CPMP/CVMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev 3, July 2011) for the manufacture of the APIs listed on the following page.

We confirm that:

- Materials used in the manufacturing processes are not of human or animal origin.
- Facilities for the processing and handling of APIs and intermediates are not used for handling components of human or animal origin.
- All non-direct process related materials such as oils, greases and cleaning agents are not of human or animal origin.

18-JULY-2019.

Dr Gavin Matthew CBiol MRSB
Director Quality Assurance / Quality Control, Scotland
Macfarlan Smith Limited

JM

Alfentanil Hydrochloride
Apomorphine Hydrochloride
Buprenorphine
Buprenorphine Hydrochloride
Cocaine
Cocaine Hydrochloride
Codeine
Codeine Sulfate
Codeine Phosphate
Diamorphine
Diamorphine Hydrochloride
Dihydrocodeine Hydrogen Tartrate
Diprenorphine
Etorphine
Fentanyl
Fentanyl Citrate
Hydromorphone Hydrochloride
Methylphenidate Hydrochloride
Morphine Hydrochloride
Morphine Sulfate
Morphine Tartrate
Naloxone Hydrochloride
Naltrexone Hydrochloride
Oxycodone Hydrochloride
Pholcodine
Remifentanil Hydrochloride
Sufentanil Citrate