

Medicines and Healthcare products Regulatory Agency

CERTIFICATE NUMBER : UK API 32496 Insp GMP 32496/30433-0030

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER(1),(2)

Part 1

Issued following an inspection in accordance with :
Regulation 331A of The Human Medicines Regulations 2012 (SI 2012/1916)

The competent authority of United Kingdom confirms the following :

The Manufacturer : AESICA QUEENBOROUGH LIMITED

Site address : AESICA QUEENBOROUGH LIMITED, NORTH ROAD, QUEENBOROUGH, ME11 5EL, UNITED KINGDOM

Is an active substance manufacturer that has been inspected in accordance with Regulation 327 of The Human Medicines Regulations 2012 (SI 2012/1916).

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 28/11/2018 , it is considered that it complies with

- The principles of GMP for active substances referred to in Regulation B17 and C17 of the Human Medicines Regulations 2012 (SI 2012/1916)

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 valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in MHRA-GMDP. If it does not appear, please contact the issuing authority.

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- (1) *Guidance on the interpretation of this template can be found in the Help menu of MHRA-GMDP database.*
 - (2) *These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products

Manufacture of active substance. Names of substances subject to inspection :

- [2000006936] LEVOBUPIVACAINE HYDROCHLORIDE
- [2000007625] CISATRACURIUM BESYLATE
- [1000007817] ISOFLURANE
- [3000013154] NALTREXONE BASE ANHYDROUS
- [2000007614] NALTREXONE HYDROCHLORIDE
- [3000010924] TRIMETHADIONE
- [2000007435] REMIFENTANIL HYDROCHLORIDE

- [4000007377] FLURBIPROFEN SODIUM DIHYDRATE
- [2000007520] BUTORPHANOL TARTRATE

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

LEVOBUPIVACAINE HYDROCHLORIDE

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.1 Manufacture Of Active Substance Intermediates
 - 3.1.2 Manufacture Of Crude Active Substance
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Crystallisation
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Drying
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging
- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing
 - 3.6.2 Microbiological testing (excluding sterility testing)

CISATRACURIUM BESYLATE

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.1 Manufacture Of Active Substance Intermediates
 - 3.1.2 Manufacture Of Crude Active Substance
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
HPLC and Precipitation
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Drying
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging
- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing
 - 3.6.2 Microbiological testing (excluding sterility testing)

ISOFLURANE

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.1 Manufacture Of Active Substance Intermediates
 - 3.1.2 Manufacture Of Crude Active Substance
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Distillation
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Drying via Freeze Tank
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging
- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing

NALTREXONE BASE ANHYDROUS

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Slurry in methanol
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Drying and Seiving
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging
- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing
 - 3.6.2 Microbiological testing (excluding sterility testing)

NALTREXONE HYDROCHLORIDE

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Hydrochloride salt formation and crystallisation
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Drying and Seiving
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging

- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing
 - 3.6.2 Microbiological testing (excluding sterility testing)

TRIMETHADIONE

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.1 Manufacture Of Active Substance Intermediates
 - 3.1.2 Manufacture Of Crude Active Substance
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Crystallisation
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Milling and Drying
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging
- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing

REMIFENTANIL HYDROCHLORIDE

- 3.1 Manufacture of Active Substance by Chemical Synthesis
 - 3.1.1 Manufacture Of Active Substance Intermediates
 - 3.1.2 Manufacture Of Crude Active Substance
 - 3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Crystallisation
- 3.5 General Finishing Steps
 - 3.5.1 Physical Processing Steps
Drying
 - 3.5.2 Primary Packaging
 - 3.5.3 Secondary Packaging
- 3.6 Quality Control Testing
 - 3.6.1 Physical / Chemical testing

FLURBIPROFEN SODIUM DIHYDRATE

- 3.1 Manufacture of Active Substance by Chemical Synthesis

3.1.1 Manufacture Of Active Substance Intermediates

3.6 Quality Control Testing

3.6.1 Physical / Chemical testing

BUTORPHANOL TARTRATE

3.1 Manufacture of Active Substance by Chemical Synthesis

3.1.1 Manufacture Of Active Substance Intermediates

3.1.2 Manufacture Of Crude Active Substance

3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Crystallisation

3.5 General Finishing Steps

3.5.1 Physical Processing Steps

Drying

3.5.2 Primary Packaging

3.5.3 Secondary Packaging

3.6 Quality Control Testing

3.6.1 Physical / Chemical testing

3.6.2 Microbiological testing (excluding sterility testing)

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| 26/02/2019 | Name and signature of the authorised person of the Competent Authority of United Kingdom |
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| | Medicines and Healthcare products Regulatory Agency |
| | Tel : Confidential |