

French National Agency for Medicines and Health Products Safety

CERTIFICATE NUMBER :16MPP050HFR03

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER ^{1, 2}

Part 1

Issued following an inspection in accordance with :

Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of France confirms the following:

The manufacturer:**EURISO-TOP**

Site address:**CEA Saclay, Bâtiment 547 Extension, Gif-sur-Yvette, 91191 CEDEX, France**

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC .

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on **2016-06-22** , it is considered that it complies with:

- The principles of GMP for active substances³ referred to in Article 47 of Directive 2001/83/EC .

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

¹ The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.

² Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.

³ These requirements fulfil the GMP recommendations of WHO.

IMPORTANT :

Due to the restrictions caused by COVID-19, the period of validity of MIA's, WDA's, GMP and GDP certificates is automatically extended until the end of 2021. On-site inspections will resume as soon as there is a consensus that the period of the public health crisis has passed. The clarifying remark section of individual MIA's, WDA's, GMP and GDP certificates will indicate any exceptions. Competent authorities reserve the right to inspect a manufacturing site should the need arise.

Part 2

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

OCTANOIC ACID [1-13C](en)

(2-OCTANOYL [1-13C]) - 1.3 DISTEAROYL GLYCEROL(en)

D-GLUCOSE [6,6-D2](en)

GLYCEROL [1,1,2,3,3-D5](en)

L-LEUCINE [1-13C](en)

L-LEUCINE [5,5,5-D3](en)

METHACETIN [METHOXY 13C](en)

UREA [13C](en)

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance :D-GLUCOSE [6,6-D2]	
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :OCTANOIC ACID [1-13C]	
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: Distillation
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :(2-OCTANOYL [1-13C]) - 1.3 DISTEAROYL GLYCEROL	
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Recrystallization

3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :GLYCEROL [1,1,2,3,3-D5]	
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: Distillation
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :L-LEUCINE [1-13C]	
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: Precipitation (pH) and washing
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :L-LEUCINE [5,5,5-D3]	
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:

	Recrystallization
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :METHACETIN [METHOXY 13C]	
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Recrystallization
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active Substance :UREA [13C]	
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Recrystallization
3.5	General Finishing Steps
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

Clarifying remarks (for public users)

see page 1 for validity

Period of validity of the certificate extended to 21/06/2020 / Signatory : Mrs Linda Gallais, head of starting materials inspection department --- The ANSM does not issue hard copies of good practices certificates

2019-09-05
see page 1 for validity

Name and signature of the authorised person of the
Competent Authority of France

Confidential
French National Agency for Medicines and Health
Products Safety
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