Italian Medicines Agency

CERTIFICATE NUMBER: ***IT-API/43/H/2024***

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 Italy confirms the following:
The manufacturer: ***Ice S.p.A.***
Site address: ***Via Novi 78, Basaluzzo, 15060, Italy***
OMS Organisation Id. / OMS Location Id.: ***ORG-100015143*** / ***LOC-100051551***

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 ***2022-12-02***, it is considered that it complies with:

- The principles of GMP for active substances [3] 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. Updates to restrictions or clarifying remarks can be identified through the EudraGMDP website (http://eudragmdp.ema.europa.eu/). 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.

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[1] *The certificate referred to in paragraph Art. 111(5) of Directive 2001/83/ECis also applicable to importers.*

[2] *Guidance on the interpretation of this template can be found in the Interpretation of the Union format for GMP certificate.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products

Manufacture of active substance. Names of substances subject to inspection:
DEOXYCHOLIC ACID(en)
SODIUM DEOXYCHOLATE(en)
SODIUM CHOLATE(en)
DEHYDROCHOLIC ACID(en)
TAUROURSODEOXYCHOLIC ACID(en)
URSODEOXYCHOLIC ACID(en)
CHENODEOXYCHOLIC ACID(en)
CHOLIC ACID(en)
N-METHYLBENZO(5,6)QUINOLINIUMMETHYLSULFATE(en)

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance:DEOXYCHOLIC ACID

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:SODIUM DEOXYCHOLATE

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.5 Modification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:SODIUM CHOLATE

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.5 Modification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:DEHYDROCHOLIC ACID

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.5 Modification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, milling, sieving
3.6	**Quality Control Testing**

	3.6.1 Physical / Chemical testing

Active Substance:TAUROURSODEOXYCHOLIC ACID

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.5 Modification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:URSODEOXYCHOLIC ACID

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.5 Modification of extracted substance Animal 3.2.7 Other: bovine, swine and chicken origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, milling, micronisation, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:CHENODEOXYCHOLIC ACID

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal

	3.2.5 Modification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, milling, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:CHOLIC ACID

3.2	**Extraction of Active Substance from Natural Sources**
	3.2.6 Purification of extracted substance Animal 3.2.7 Other: bovine origin
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying, sieving
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance:N-METHYLBENZO(5,6)QUINOLINIUMMETHYLSULFATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: purification,crystallisation
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: drying,sieving

3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

4. Other Activities - Active Substances:
Importation of: CHENODEOXYCHOLIC ACID CRUDE (confidential), CHOLIC ACID CRUDE (confidential), DEOXYCHOLIC ACID CRUDE (confidential), HYODEOXYCHOLIC ACID CRUDE (confidential), URSODEOXYCHOLIC ACID CRUDE (confidential), N-methylbenzo(5,6)quinolinium methyl sulfate crude (confidential)

Clarifying remarks (for public users)

According to Italian legislation, all the biological AS and/or active substances deriving from human and animal tissues, organs, fluids are authorized according to art. 40 of Dir. 2001/83/EC.Imported raw ursodeoxycholic acid is bovine and chicken origin. Imported raw deoxycholic acid is bovine origin. Imported chenodeoxycholic acid is swine origin. Imported active substances (AS) marked as confidential undergo further processing within the importing site and/or are released to other AS manufacturing sister companies for processing. On a risk-based approach, the validity of the GMP certificate for this manufacturing site is not more than 36 months from the latest general GMP inspection conducted on 2022/12/02, except for AIFA¿s re-evaluation of the risk profile.

2024-02-28

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

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Confidential
Agenzia Italiana del Farmaco
Tel:***Confidential***
Fax:***Confidential***