AGENZIA ITALIANA DEL FARMACO

Certificate No: IT-API/58/H/2019

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC

The competent authority of Italy confirms the following:
The manufacturer BIOINDUSTRIA LABORATORIO ITALIANO MEDICINALI S.P.A.
Site address Via della Giustizia, 1 - 15064 FRESONARA (AL)

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation: **D.L. n. 219 of 24th April 2006 art. 53**

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 2018/06/21, it is considered that it complies with the Good Manufacturing Practice requirements referred to in the principles of GMP for active substances 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.
The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

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SIS : 823

AGENZIA ITALIANA DEL FARMACO

Part 2

Name and address of the site:

BIOINDUSTRIA LABORATORIO ITALIANO MEDICINALI S.P.A. - Via della Giustizia, 1, 15064 FRESONARA (AL)

Name of the active Substances manufactured or imported:

ETACRYNIC ACID
AMILORIDE HYDROCHLORIDE DIHYDRATE
BACLOFEN
DOBUTAMINE HYDROCHLORIDE
GABEXATE MESILATE
INDAPAMIDE
LEVODROPROPIZINE
METHYLTHIONINIUM CHLORIDE
DISODIUM PAMIDRONATE PENTAHYDRATE
PRAZOSIN HYDROCHLORIDE
S-BENZYLOXYMETHYL THIAMINE
SILDENAFIL CITRATE
TAMSULOSIN HYDROCHLORIDE
TERAZOSIN HYDROCHLORIDE DIHYDRATE
TORASEMIDE
TRIPROLIDINE HYDROCHLORIDE

3 - Manufacturing Operations - Active Substances

ETACRYNIC ACID

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:

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	crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

3 - Manufacturing Operations - Active Substances

AMILORIDE HYDROCHLORIDE DIHYDRATE

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: salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

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3 - Manufacturing Operations - Active Substances BACLOFEN	
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: crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

3 - Manufacturing Operations - Active Substances DOBUTAMINE 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: salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps

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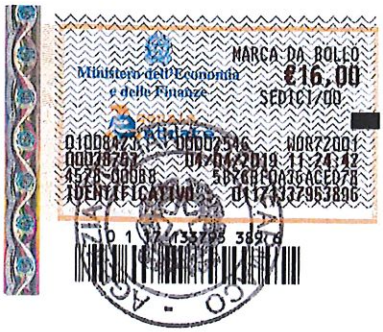

	drying, milling **3.5.2.** Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) **3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any 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

3 - Manufacturing Operations - Active Substances

GABEXATE MESILATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2. Manufacture of crude active substance **3.1.3.** Salt formation / Purification steps: salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying **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

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3 - Manufacturing Operations - Active Substances INDAPAMIDE	
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: crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling, micronisation **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

3 - Manufacturing Operations - Active Substances LEVODROPROPIZINE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2. Manufacture of crude active substance **3.1.3.** Salt formation / Purification steps: crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps

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	drying, milling **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

3 - Manufacturing Operations - Active Substances

METHYLTHIONINIUM CHLORIDE

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: crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying,milling **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

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3 - Manufacturing Operations - Active Substances

DISODIUM PAMIDRONATE PENTAHYDRATE

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: salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

3 - Manufacturing Operations - Active Substances

PRAZOSIN HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2. Manufacture of crude active substance **3.1.3.** Salt formation / Purification steps: salt formation, purification
3.5	**General Finishing Steps**

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	3.5.1. Physical processing steps drying, milling **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

3 - Manufacturing Operations - Active Substances

S-BENZYLOXYMETHYL THIAMINE

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: crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

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3 - Manufacturing Operations - Active Substances

SILDENAFIL CITRATE

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: salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

3 - Manufacturing Operations - Active Substances

TAMSULOSIN HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2. Manufacture of crude active substance **3.1.3.** Salt formation / Purification steps: salt formation, crystallisation

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3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling, micronisation **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

3 - Manufacturing Operations - Active Substances

TERAZOSIN HYDROCHLORIDE DIHYDRATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2. Manufacture of crude active substance **3.1.3.** Salt formation / Purification steps: salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

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3 - Manufacturing Operations - Active Substances

TORASEMIDE

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: crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling **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

3 - Manufacturing Operations - Active Substances

TRIPROLIDINE 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:

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	salt formation, crystallisation
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, milling/micronisation **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

Restrictions or clarifying remarks:

Imported active substances marked as confidential undergo further processing within the importing site. The active substance Torasemide is manufactured in two polymorphic form (form I and form II). The Inspectorate adopted a risk-based approach for planning of inspections, therefore the validity of the GMP certificate for this manufacturing site is not more than 36 months from the last general GMP inspection, which was conducted on 2018/06/21. It will still be AIFA¿s right to re-evaluate the validity of the GMP certificate based on risk profile changes.

Rome, 2019/03/29

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

Dott.ssa Marisa Delbò
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