Agenzia Italiana del Farmaco

AIFA

Certificate No: IT-API/6/H/2017

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 LUSOCHIMICA S.P.A.
Site address VIA GIOTTO, 9 - 23871 LOMAGNA (LC)

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 2016/08/31, 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.

AIFA - Italian Medicines Agency
GMP Inspections and Manufacturing Authorizations of APIs Office
Via del Tritone, n° 181 - 00187 ROMA (ITALY)
Tel.+390659784409 Fax +390659784617
website: www.agenziafarmaco.it
SIS : 1744

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Agenzia Italiana del Farmaco

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Part 2

Name and address of the site:

LUSOCHIMICA S.P.A. - VIA GIOTTO, 9, 23871 LOMAGNA (LC)

Name of the active Substances manufactured or imported:

BARNIDIPINE HYDROCHLORIDE
BETAXOLOL HYDROCHLORIDE
BRIVUDINE
CARTEOLOL HYDROCHLORIDE
DIHYDROXY DIBUTYL ETHER
DILTIAZEM HYDROCHLORIDE
DILTIAZEM RESINATE
FENOTEROL HYDROBROMIDE
FORMOTEROL FUMARATE DIHYDRATE
IPRATROPIUM BROMIDE
IPRAZOCHROME
ISOPRENALINE SULFATE
ISOXSUPRINE HYDROCHLORIDE
ISOXSUPRINE HYDROCHLORIDE CRUDE
MANIDIPINE DIHYDROCHLORIDE
NAFTIFINE HYDROCHLORIDE
NICARDIPINE HYDROCHLORIDE
NIMODIPINE
NISOLDIPINE
NITRENDIPINE
ORCIPRENALINE SULFATE
PRAMIRACETAM SULFATE
REPROTEROL HYDROCHLORIDE
RITODRINE HYDROCHLORIDE
SALBUTAMOL SULFATE
SULFADIAZINE
SULFADIAZINE SILVER
TERBUTALINE SULFATE
TOLNAFTATE
TOLNAFTATE CRUDE
ZOFENOPRIL CALCIUM

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3 - Manufacturing Operations - Active Substances

BARNIDIPINE 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: 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

3 - Manufacturing Operations - Active Substances

BETAXOLOL 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:

	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

3 - Manufacturing Operations - Active Substances

BRIVUDINE

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 granulation,drying **3.5.2.** Primary Packaging (enclosing / sealing the active substance within a packaging material which is indirect 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**

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	3.6.1. Physical / Chemical testing

3 - Manufacturing Operations - Active Substances

CARTEOLOL 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**
	3.5.1. Physical processing steps granulation,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

3 - Manufacturing Operations - Active Substances

DIHYDROXY DIBUTYL ETHER

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	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)
3.6	**Quality Control Testing**
	3.6.1. Physical / Chemical testing

3 - Manufacturing Operations - Active Substances

DILTIAZEM 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: 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

3 - Manufacturing Operations - Active Substances

DILTIAZEM RESINATE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4. Other adsorption on resin
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

3 - Manufacturing Operations - Active Substances

FENOTEROL HYDROBROMIDE

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 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

3 - Manufacturing Operations - Active Substances

FORMOTEROL FUMARATE 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: 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

3 - Manufacturing Operations - Active Substances

IPRATROPIUM BROMIDE

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 granulation,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

3 - Manufacturing Operations - Active Substances

IPRAZOCHROME

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 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

3 - Manufacturing Operations - Active Substances

ISOXSUPRINE HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3. Salt formation / Purification steps: 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

3 - Manufacturing Operations - Active Substances

MANIDIPINE DIHYDROCHLORIDE

3.5	**General Finishing Steps**
	3.5.4. Other

	batch certification
3.6	**Quality Control Testing**
	3.6.1. Physical / Chemical testing

3 - Manufacturing Operations - Active Substances

NAFTIFINE 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: purification
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

3 - Manufacturing Operations - Active Substances

NICARDIPINE 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: 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

3 - Manufacturing Operations - Active Substances

NIMODIPINE

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 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

3 - Manufacturing Operations - Active Substances

NISOLDIPINE

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 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

3 - Manufacturing Operations - Active Substances

NITRENDIPINE

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 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

3 - Manufacturing Operations - Active Substances

ORCIPRENALINE SULFATE

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 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

3 - Manufacturing Operations - Active Substances

PRAMIRACETAM SULFATE

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

3 - Manufacturing Operations - Active Substances

REPROTEROL 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:

	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

3 - Manufacturing Operations - Active Substances

RITODRINE 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: 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

3 - Manufacturing Operations - Active Substances SALBUTAMOL SULFATE	
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 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

3 - Manufacturing Operations - Active Substances SULFADIAZINE SILVER	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3. Salt formation / Purification steps: salt formation
3.5	**General Finishing Steps**

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	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

3 - Manufacturing Operations - Active Substances

TERBUTALINE SULFATE

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 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

TOLNAFTATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3. Salt formation / Purification steps: 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

3 - Manufacturing Operations - Active Substances

ZOFENOPRIL CALCIUM

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1. Manufacture of active substance intermediates **3.1.3.** Salt formation / Purification steps: 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

4. Other Activities - Active Substance:

Importation of:
ISOPRENALINE SULFATE (Confidential); ISOXSUPRINE HYDROCHLORIDE CRUDE (Confidential); SULFADIAZINE (Confidential); TOLNAFTATE CRUDE (Confidential)

Restrictions or clarifying remarks:

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 42 months from the last general GMP inspection, which was conducted on (2015/09/18). It will still be AIFA¿s right to re-evaluate the validity of the GMP certificate based on risk profile changes.Imported active substances marked as confidential undergo further processing within the importing site.

Rome, 2017/01/18

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

Dott.ssa Isabella Marta
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