Agenzia Italiana del Farmaco

CERTIFICATE NUMBER: ***IT-API/18/H/2016***

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: ***LUSOCHIMICA S.P.A.***
Site address: ***VIA GIOTTO, 9, LOMAGNA, 23871, Italy***

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 ***2015-09-18*** , 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. 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 EudraGMP. 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.*

Part 2

Human Medicinal Products

Manufacture of active substance. Names of substances subject to inspection :
NISOLDIPINA(it) / NISOLDIPINE(en)
IPRATROPIO BROMURO(it) / IPRATROPIUM BROMIDE(en)
DILTIAZEM RESINATO(it) / DILTIAZEM RESINATE(en)
BETAXOLOLO CLORIDRATO(it) / BETAXOLOL HYDROCHLORIDE(en)
DIIDROSSI DIBUTIL ETERE(it) / DIHYDROXY DIBUTYL ETHER(en)
ZOFENOPRIL CALCIO(it) / ZOFENOPRIL CALCIUM(en)
BRIVUDIN(it) / BRIVUDINE(en)
FENOTEROLO BROMIDRATO(it) / FENOTEROL HYDROBROMIDE(en)
NAFTIFINA CLORIDRATO(it) / NAFTIFINE HYDROCHLORIDE(en)
NIMODIPINA(it) / NIMODIPINE(en)
PRAMIRACETAM SOLFATO(it) / PRAMIRACETAM SULFATE(en)
REPROTEROLO CLORIDRATO(it) / REPROTEROL HYDROCHLORIDE(en)
RITODRINA CLORIDRATO(it) / RITODRINE HYDROCHLORIDE(en)
SULFADIAZINA ARGENTICA(it) / SULFADIAZINE SILVER(en)
BARNIDIPINA CLORIDRATO(it) / BARNIDIPINE HYDROCHLORIDE(en)
NICARDIPINA CLORIDRATO(it) / NICARDIPINE HYDROCHLORIDE(en)
ORCIPRENALINA SOLFATO(it) / ORCIPRENALINE SULFATE(en)
IPRAZOCROMO(it) / IPRAZOCHROME(en)
TERBUTALINA SOLFATO(it) / TERBUTALINE SULFATE(en)
MANIDIPINA DICLORIDRATO(it) / MANIDIPINE DIHYDROCHLORIDE(en)
CARTEOLOLO CLORIDRATO(it) / CARTEOLOL HYDROCHLORIDE(en)
SALBUTAMOLO SOLFATO(it) / SALBUTAMOL SULFATE(en)
DILTIAZEM CLORIDRATO(it) / DILTIAZEM HYDROCHLORIDE(en)
FORMOTEROLO FUMARATO DIIDRATO(it) / FORMOTEROL FUMARATE DIHYDRATE(en)
NITRENDIPINA(it) / NITRENDIPINE(en)

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance : NISOLDIPINE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**

	3.6.1 Physical / Chemical testing

Active Substance : IPRATROPIUM BROMIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
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 : granulation,drying
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : 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 3.5.3 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : BETAXOLOL HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : DIHYDROXY DIBUTYL ETHER

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

Active Substance : ZOFENOPRIL CALCIUM

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.1 Manufacture of active substance intermediates
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : BRIVUDINE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance 3.1.1 Manufacture of active substance intermediates
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 : granulation,drying
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : FENOTEROL HYDROBROMIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : NAFTIFINE HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : purification 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : NIMODIPINE

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

	3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : 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 3.5.3 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : REPROTEROL HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : RITODRINE HYDROCHLORIDE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing
Active Substance : 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**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing
Active Substance : BARNIDIPINE HYDROCHLORIDE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance 3.1.1 Manufacture of active substance intermediates
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : NICARDIPINE HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : ORCIPRENALINE SULFATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : IPRAZOCHROME

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

3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : TERBUTALINE SULFATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : MANIDIPINE DIHYDROCHLORIDE

3.5	**General Finishing Steps**
	3.5.4 Other : batch certification
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : 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**
	3.5.3 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 : granulation,drying
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : SALBUTAMOL SULFATE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : DILTIAZEM HYDROCHLORIDE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : FORMOTEROL FUMARATE DIHYDRATE

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

	3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

Active Substance : NITRENDIPINE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : crystallisation 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing

4. Other Activities - Active Substances :
Importation of: ISOPRENALINE SULFATE (confidential), ISOXSUPRINE HYDROCHLORIDE (confidential), SULFADIAZINE (confidential), TOLNAFTATE (confidential)

Clarifying remarks (for public users)

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.

2016-03-18 Name and signature of the authorised person of the

Competent Authority of Italy

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