sa Alcon-Couvreur nv
Rijksweg 14, 2870 Puurs, Belgium
T: +32 3 890 27 11 - F: +32 3 890 27 17
RPR Mechelen - VAT: BE0402134977

Alcon®

CERTIFICATE

The undersigned, E. Merken, RA Manager RA Product/Plant Support & Submissions Management of sa Alcon-Couvreur nv, Rijksweg 14, 2870 Puurs / Belgium, hereby confirms that the attached document is a copy of the Certificate of GMP Compliance issued following an inspection of the Competent Authority of the Republic of Italy at

SICOR SOCIETA' ITALIANA CORTICOSTEROIDI S.R.L.
Inspection date 6th November 2015,
Strada Briantea km. 36 n. 83 -23892 BULCIAGO (LC)
ITALY

This certificate may not be reproduced and is solely destined to the Governmental Authorities of CHILE.

sa Alcon-Couvreur nv
September 2016

p.p. De Schepper

Caroline De Schepper
RA Coordinator Submissions Management

E. Merken,
Manager RA Product/Plant Support & Submissions Management

Seen for legalization of
the signature of
Caroline De Schepper

Antwerpen, 06/10/2016

Notary Public

a Novartis company

B 00001469

B 00001469

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Land/Pays/Land : ***BELGIË – BELGIQUE – BELGIEN.***

2. Deze openbare akte is ondertekend door :
Le présent acte public a été signé par : ***Kiebooms, Johan***
Diese öffentliche Urkunde ist unterschrieben von:

3. Handelend in hoedanigheid van :
Agissant en qualité de : ***Notaris/Notaire/Notar***
In seiner/ihrer Eigenschaft als:

4. Is voorzien van het zegel van
Est revêtu du sceau de ***Notaris/Notaire/Notar Antwerpen***
Sie ist versehen mit dem Siegel des/der:

Voor echt verklaard / Attesté / Bestätigt

5. ***Te Brussel/A Bruxelles/In Brüssel*** 6. Op/Le/Am : ***12/10/2016***

7. Door FOD Buitenlandse Zaken, Buitenlandse Handel en Ontwikkelingssamenwerking
Par le SPF Affaires étrangères, Commerce extérieur et Coopération au Dévelopement
Durch FOD Auswärtige Angelegenheiten, Außenhandel und Entwicklungszusammenarbeit

8. Onder Nr. /Sous le n°/ Unter Nr. : ***9805367434926960***

9. Stempel/Sceau/Stempel :

10. Ondertekening/Signature/ Unterschrift :

Jan Van de Velde

Prijs/Prix/ Preis : ***20*** EUR

Deze Apostille waarborgt de authenticiteit van de inhoud van het document niet.
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Agenxia Italiana del Farmaco

AIFA

Certificate No: IT-API/62/H/2016

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 SICOR SOCIETA' ITALIANA CORTICOSTEROIDI S.R.L.
Site address Strada Briantea km. 36 n. 83 - 23892 BULCIAGO (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 2015/11/06, 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
Manufacturing Authorization Office
Via del Tritone, n° 181 - 00187 ROMA (ITALY)
Tel.+390659784489 Fax +390659784312
website: www.agenziafarmaco.it
SIS : 1007

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Part 2

Name and address of the site:

SICOR SOCIETA' ITALIANA CORTICOSTEROIDI S.R.L. - Strada Briantea km. 36 n. 83, 23892 BULCIAGO (LC)

Name of the active Substances manufactured or imported:

ACICLOVIR
ACICLOVIR CRUDE
ALENDRONIC ACID
ATOMOXETINE HYDROCHLORIDE
CARBIDOPA
DL-NAPROXEN
LABETALOL HYDROCHLORIDE
LEVODOPA
LEVODOPA CRUDE
METHYLDOPA
METOPROLOL TARTRATE
NAPROXEN
NAPROXEN SODIUM
PRASTERONE CRUDE
TIMOLOL MALEATE
VALACICLOVIR HYDROCHLORIDE
VERAPAMIL HYDROCHLORIDE

3 - Manufacturing Operations - Active Substances

ACICLOVIR

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 **ALENDRONIC 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: 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 **ATOMOXETINE 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

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	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 **CARBIDOPA**	
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, sieving **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 LABETALOL 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: salification, cristallisation
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 LEVODOPA	
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, sieving 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

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	3.6.1. Physical / Chemical testing

3 - Manufacturing Operations - Active Substances **METHYLDOPA**	
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, sieving **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 **METOPROLOL TARTRATE**	
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 **NAPROXEN**	
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, sieving 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 **NAPROXEN SODIUM**	
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
3.5	**General Finishing Steps**
	3.5.1. Physical processing steps drying, sieving

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	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 **PRASTERONE CRUDE**	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1. Manufacture of active substance intermediates Special Requirements Other: Hormones or substances with hormonal activity **3.1.2.** Manufacture of crude active substance
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 **TIMOLOL MALEATE**	
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
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 VALACICLOVIR 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, 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 VERAPAMIL 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 drying, sieving 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:
ACICLOVIR CRUDE (Confidential); DL-NAPROXEN (Confidential); LEVODOPA CRUDE (Confidential)

Restrictions or clarifying remarks:

Imported APIs marked as confidential undergo further processing within the importing site.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 2015/11/6.It will still be AIFA's right to re-evaluate the validity of the GMP certificate based on risk profile changes.

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MARCA DA BOLLO
€16,00
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00028450 00002C84 W114U0D1
00017992 23/03/2016 09:43:08
4578-00088 D3CB0B19652ED4FA
IDENTIFICATIVO : 01131956162187
0 1 13 195616 218 7

Agenzia Italiana del Farmaco

AIFA

Rome, 2016/07/19

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

Dott.ssa Isabella Marta
AIFA – Manufacturing Authorization Office

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