Ministry of Health, Welfare and Sport
CIBG
P.O. Box 16113
2500 BC Den Haag
The Netherlands

Certificate of a Pharmaceutical Product[1]

This certificate conforms to the format recommended by the World Health Organization.
(Explanatory Notes and General Instructions attached)

Exporting (certifying) country: **The Netherlands** No. of Certificate: 19-1691

Importing (requesting) country: **Chile**

1. Name and dosage form of product
Name (Netherlands): Clozapine 100 mg, tabletten
Name (Chile): Lodux comprimidos 100 mg
Dosage form: Tablets
Legal status: Prescription only medicine

1.1 Active ingredient(s)[2] and amount(s) per unit dose[3].
100 mg Clozapine per tablet
For complete composition including excipients see appendix 1 of this certificate

1.2 Is this product licensed to be placed on the market for use in The Netherlands?[4]
(a) yes/no **YES** (b) application pending: yes/no **NO**

1.3 Is this product on the market in The Netherlands? Yes/no/unknown **YES**

2A.1 Number of product licence[6] and date of issue:
RVG21825, 08.09.1998

2A.2 Product licence holder (name and address):
Genthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

2A.3 Status of product licence holder[7] : a/ b/ c/ **C**

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form is:[8]
Synthon Hispania S.L.
C/Castello 1
08830 Sant Boi de Llobregat (Barcelona)
Spain
(DP Manufacturer, Release site, Primary and secondary packager)

Rottendorf Pharma GmbH
Ostenfelderstrasse 51-61
D-59320 Ennigerloh Nordrhein-Westfale
Germany
(DP Manufacturer, Release site, Primary and secondary packager)

2A.4 Is summary basis of approval appended?[9] yes/no **NO**

2A.5 Is officially approved product information, complete and consonant with the license, attached? yes/ no/ not provided [10] **YES**

For approved product information please refer to appendix 2 of this certificate

2A.6 Applicant for certificate, if different from licence holder (name and address)[11]:
Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

3. Does the Netherlands' certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?
No. The facilities outside the territory of The Netherlands' certifying authority are inspected by the local competent authority.

4. Does the information submitted by the applicant satisfy the Netherlands' certifying authority on all aspects of the manufacture of the product[15]?
Yes

.....
.....

Address of certifying authority:

Ministry of Health, Welfare and Sport
CIBG
P.O. Box 16114
2500 BC Den Haag, the Netherlands

Name of authorized person:

dr. M.J. van de Velde, PhD

Signature:

.....

Stamp and date:

19 DEC. 2019

1. Please refer to th
of the scheme.

2. The forms are suit

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

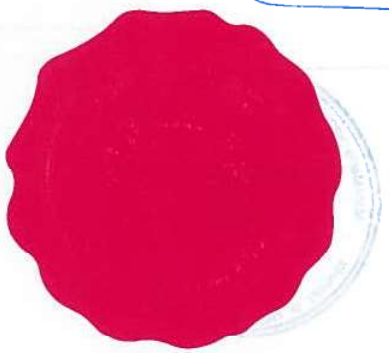
1. Country: THE NETHERLANDS
   This public document
2. has been signed by **dr. M.J. van de Velde**
3. acting in the capacity of Registrar of Medical Professions
4. bears the seal/stamp of the Ministry of Health, Welfare and Sport

Certified

5. in Arnhem
6. on 16-01-2020
7. by the registrar of the district court of Gelderland
8. no. 20.119

9. Seal/stamp:
10. Signature:

S.R. Nolten



3.2.P.1 Description and Composition of the Drug Product

Description of the drug product

Yellow, round tablets, scored with a division mark on both sides and debossed with CPN 100 on one side.

Ingredients	Mass per *tablet* [1] [mg]	Quality	Function
Clozapine		Ph. Eur.	active
Lactose monohydrate		Ph. Eur.	diluent
Povidone		Ph. Eur.	binder
Pregelatinized starch		Ph. Eur.	diluent/disintegrant
Maize starch		Ph. Eur.	diluent/disintegrant
Talc		Ph. Eur.	glidant/lubricant
Colloidal anhydrous silica		Ph. Eur.	glidant
Magnesium stearate[2]		Ph. Eur.	lubricant
Total mass			

1 The acceptance limits for the drug substance are 95-105 % from the nominal value and 90-110 % from the nominal value for the excipients, in accordance with the NfG "Manufacturing of the Finished Dosage Form" (CPMP/QWP/486/95).

2 Vegetable origin

Container

The tablets are available in PVC/PVDC/Al blisterss (packed in boxes) or in HDPE containers with an aluminium seal and child-resistant (PP) closure.

For detailed information on the packaging materials please refer to Module 3 - Section 2.P.7 of the CTD (Common Technical Document).

Ministerie van Volksgezondheid, Welzijn en Sport
Ministry of Health, Welfare and Sport

Josep Altés MAY 2 3 2019

Qualified Person

1.3.1 Summary of Product Characteristics - Core

Clozapine can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who are non-responsive to or intolerant of antipsychoticmedication, or with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1)**
- **who have initially normal leukocyte findings (white blood cell count $\geq 3500/mm^3$ ($\geq 3.5x10^9/l$), and ANC $\geq 2000/mm^3$ ($\geq 2.0x10^9/l$)), and**
- **in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of treatment, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of clozapine (see section 4.4).**

Prescribing physicians must comply fully with the required safety measures. At each consultation, a patient receiving clozapine must be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention must be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see section 4.4).

Clozapine must be dispensed under strict medical supervision in accordance with official recommendations (see section 4.4).

<u>Myocarditis</u>

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely (see section 4.4).

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction (see section 4.4).

If myocarditis or cardiomyopathy are suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist (see section 4.4).

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine (see section 4.3 and 4.4).

1. NAME OF THE MEDICINAL PRODUCT

<Clozapine 25 mg, tablets>
<Clozapine 50 mg, tablets>
<Clozapine 100 mg, tablets>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg clozapine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Silica, colloidal anhydrous
Povidone
Talc
Maize starch
Lactose monohydrate
Pregelatinised starch

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

5 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

<Clozapine tablets> are packaged in PVC/PVDC/aluminium blisters. The blisters are packaged in pack sizes of 7, 14, 20, 28, 30, 40, 50, 60, 84, 90, 100 and 300 tablets in a lithographed carton box.
<Clozapine tablets> are also available in lithographed carton boxes containing 50 tablets in a perforated unit dose blister for hospital use - PVC/PVDC/Al blister.
In addition, <Clozapine tablets> are available in HDPE containers of 7, 14, 28, 30, 40, 50, 60, 84, 90, 100, 250, 300, 500, 1000, 1500 and 2500 tablets, with a child-resistant polypropylene closure.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

Appendix 3

To whom it may concern

CERTIFICATE OF PHARMACEUTICAL PRODUCT

Name and dosage form of the product in the Netherlands:
Clozapine 25/100 mg, tabletten

Name and dosage form of the product in English core Summary of Product Characteristics:
Clozapine 25/100 mg, tablets

The attached Summary of Product Characteristics (SmPC) is the English translation of the current national SmPC approved by the Health Authorities in the Netherlands.

Genthon BV
Marjolijn van der Star
Head Regulatory Affairs Maintenance

Ministerie van Volksgezondheid, Welzijn en Sport
Ministry of Health, Welfare and Sport