21.208

Ministry of Health, Welfare and Sport
CBG
P.O. Box 16114
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: 21-01472

Importing (requesting) country: **Chile**

1. Name and dosage form of product

Name (Netherlands):	**Anastrozol Synthon**
Dosage form:	**1 mg, film coated tablet**
Legal status:	**Prescription Only Medicine**
Name (Chile):	**Madelen comprimidos recubiertos 1 mg**

1.1 Active ingredient(s)[2] and amount(s) per unit dose[3].
1 mg Anastrozole per film-coated tablet.
For complete composition including excipients see appendix 1 to this certificate

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

1.3 Is this product on the market in The Netherlands? **Yes**

2A.1 Number of product licence[6] and date of issue:
RVG 34003, 3 October 2007

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

2A.3 Status of product licence holder[7] : **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/Castelló, 1
08830 Sant Boi de Llobregat (Barcelona)
Spain
(Manufacturing site, Packaging site, Release site)

2A.4 Is summary basis of approval appended?[9] **No**

2A.5 Is officially approved product information, complete and consonent with the licence, attached? **Yes**[10]
For approved product information please refer to appendix 2 to this certificate

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:
.....

11 OKT. 2021
Stamp and date:
.....

1. Please refer to t
of the scheme.
2. The forms are su
3.

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

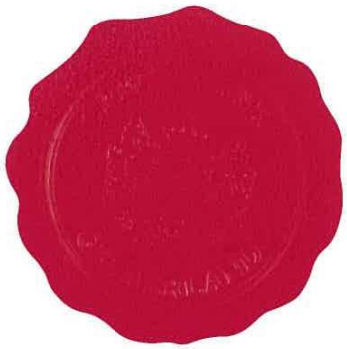
1. Country: THE NETHERLANDS
   This public document
2. has been signed by **dr. M.J. van de Velde**
3. acting in the capacity of Registrar of Medical Professions
4. bears the seal/stamp of the Ministry of Health, Welfare and Sport

Certified

5. in Arnhem 6. on 18-10-2021
7. by the registrar of the district court of Gelderland
8. no. 21-2974

9. Seal/stamp: 10. Signature:

C. Boers



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

Description of the drug product

White film-coated round biconvex tablets, debossed with "ANA" and "1" on one side

Composition of the drug product

Ingredients	Mass per tablet (mg)	Function	Quality
Core			
Anastrozole [1]	1.0	Drug substance	In-house monograph (CASS.NUS.ANA)
Lactose monohydrate [2]		Filler/diluent	Ph.Eur.
Sodium starch glycolate		Disintegrant	Ph.Eur.
Povidone		Binder	Ph.Eur.
Magnesium stearate [3]		Lubricant	Ph.Eur.
Total core mass			
Coating Ingredients			
Macrogol (PEG 400) [4]		Plasticizer	Ph.Eur.
Hypromellose (HPMC) [4]		Film forming agent	Ph.Eur.
Titanium dioxide [4]		Opacifier	Ph.Eur.
Purified water [5]		Suspension liquid	Ph.Eur.
Total tablet mass			

[1] Correction factor

Prior to manufacturing, a correction factor is calculated by the QA/QC department to compensate for free water content (L, by KF), residual solvents (RS, by GC) and assay (assay, by HPLC) of anastrozole with the following equation:

$$F = \frac{100}{100 - L\,(\text{in }\%) - RS\,(\text{in }\%)} \times \frac{100}{\text{assay}\,(\text{in }\%)}$$

When the assay of anastrozole drug substance (HPLC) is >100.0 %, then 100.0 % has to be used in the equation above.

2 Lactose monohydrate is used to compensate for the mass change of the theoretical anastrozole amount. The compensation mass of lactose monohydrate (C) is defined as:

$$C = [\text{Theoretical mass of ANA}] \times [F - 1]$$

The amount of Cis deducted from the theoretical mass of lactose monohydrate.

3 Magnesium stearate is vegetable based.

4 The combination of the excipients macrogol, hypromellose and titanium dioxide is equivalent to the ready-to-use white coating mixture Opadry Y-1-7000 from the company Colorcon.

5 Purified water is removed during the coating/drying process.

Type of closure of the dosage form

The primary packaging material is an opaque PVC/PE/PVDC/Al blister. This blister consists of 250 µm thick PVC foil, 25 µm thick PE foil, with a PVDC coating of 90 g/m^2 welded on an internally film coated 20 µm aluminium semi rigid support.

Signature:

Josep Altés
Qualified person

Ministry of Health, Welfare and Sport

1.3.1 Summary of Product Characteristics - Core

1. NAME OF THE MEDICINAL PRODUCT

[Anastrozole] film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg anastrozole.

Excipient with known effect:
Each film-coated tablet contains 93 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White film-coated round biconvex tablets, debossed with "ANA" and "1" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anastrozole is indicated for the:

- Treatment of hormone receptor-positive advanced breast cancer in postmenopausal women.
- Adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women.
- Adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

4.2 Posology and method of administration

Posology

The recommended dose of anastrozole for adults including the elderly is one 1 mg tablet once a day.

For postmenopausal women with hormone receptor-positive early invasive breast cancer, the recommended duration of adjuvant endocrine treatment is 5 years.

The survival of litters born to rats given anastrozole at 0.02 mg/kg/day and above (from Day 17 of pregnancy to Day 22 post-partum) was compromised. These effects were related to the pharmacological effects of the compound on parturition. There were no adverse effects on behaviour or reproductive performance of the first generation offspring attributable to maternal treatment with anastrozole.

Carcinogenicity

A two-year rat oncogenicity study resulted in an increase in incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males at the high dose (25 mg/kg/day) only. These changes occurred at a dose which represents 100-fold greater exposure than occurs at human therapeutic doses, and are considered not to be clinically relevant to the treatment of patients with anastrozole.

A two-year mouse oncogenicity study resulted in the induction of benign ovarian tumours and a disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in females and more deaths as a result of lymphomas). These changes are considered to be mouse-specific effects of aromatase inhibition and not clinically relevant to the treatment of patients with anastrozole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Sodium starch glycolate (type A)
Povidone (K31) (E1201)
Magnesium stearate (E572)

Film-coating
Macrogol 400
Hypromellose (E464)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Synthon

Annex 3

To whom it may concern

CERTIFICATE OF PHARMACEUTICAL PRODUCT

Name and dosage form of the product in the Netherlands:
Anastrozol Synthon 1 mg, filmomhulde tabletten

Name and dosage form of the product in English core Summary of Product Characteristics:
Anastrozole 1 mg, film-coated 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.

Synthon BV
Marjolijn van der Star
Head Regulatory Affairs Maintenance