Radboudumc

Subject: Flucytosine (ancotil ®) intravenous solution shortage resolution

Dear colleague,

We are all aware of the current drug shortage of **Flucytocine (Ancotil ®) intravenous solution** which significantly impacts quality of treatment in specific fungal infections.

The cause of the shortage is bankruptcy of the contract manufacturer of Mylan/Viatris due to quality issues in the manufacturing process. As per latest information, it may take 2 to 3 years before a new manufacturer will be approved under EMA regulations.

To cover our patient's needs, Dr. Roger Brüggemann (Radboud university medical center) has requested A15 pharmacy to make a generic copy of Ancotil available as compounded drug product.

A15 Pharmacy is a purpose-driven compounding pharmacy in equal ownership of four Dutch academic hospitals. Recently we concluded our product development successfully, in close collaboration with Mylan (MA holder). The first-lot-to-stock was produced and released for clinical use beginning January 2022. The product meets pharmacopeial standards and is manufactured within our GMP quality system which is certified under EU manufacturing authorisation 6143 F.

Given the clinical need for this product A15 Pharmacy is willing to also look into opportunities to make **Flucytosine 2500 mg = 250 mL** available for patients in Europe. A15 Pharmacy is open to support hospitals in Europe as much as we can.

In case you have a clinical need for this product, the contact details for can be found below. Your local pharmacist is invited to make arrangements.

Yours sincerely,

Dr. Reinout C.A. Schellekens,

Chief Pharmacist, Apotheek A15

Contact information:	**Product information:**
A15 Pharmacy (www.apotheeka15.nl) Team Sales & Distribution Mail: verkoop@apotheeka15.nl Phone: +31-183-820.843	Flucytosine 2500 mg = 250 mL Expiry term: 12 months Storage & Transportation conditions: 18-25 °C Unit of sale: 15 bottles (1 box) Price: € 200,= per bottle ex works (Incotherms) Product Information Sheet, Certificate of Analysis, GMP certificate available upon request. The customer is advised to contact their national authority to arrange approval of import of this non-registered drug product

Ministry of HEALTH, WELFARE and SPORT
CIBG
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: 22-00940

Importing (requesting) country: Italy

1. Name and dosage form of product

Flucytosine infusion 10 mg/ml, bottle 250 ml

1.1 Active ingredient(s)[2] and amount(s) per unit dose[3].

For complete composition including excipients see attached.

Flucytosine 2.5 g, sodium chloride 1.85 g, trometamol 305 mg, hydrochloric acid 4M approx. 0.5 ml, water for injections ad 250 ml
(complete composition per bottle containing 250 ml)

1.2 Is this product licensed to be placed on the market for use in The Netherlands?[4]

(a) No (b) application pending: No

1.3 Is this product on the market in The Netherlands? No

Not as a licensed product but as an unregistered stock preparation.

If the answer to 1.2 (a) or 1.2 (b) is yes, continue with section 2A and omit section 2B;
If the answer to 1.2 (a) or 1.2 (b) is no, omit section 2A and continue with section 2B.[5]

2B.1 Applicant for certificate (name and address):

Apotheek A15 B.V.
Buys Ballotstraat 2
4207 HT Gorinchem, The Netherlands

2B.2 Status of applicant: a

2B.2.1 For categories b and c the name and address of the manufacturer producing the dosage form is:[8]

Not applicable

2B.3 Why is marketing authorization lacking?

Not required for pharmacy preparations in The Netherlands

2B.4 Remarks[12] : There is a marketing authorization holder (Mylan Healthcare B.V.) of a registered product (Ancotil) but that MA-holder is unable to supply the market due to bankruptcy of their Swiss contract manufacturer.

3. Does the Netherlands' certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?

Yes

3.1 Periodicity of routine inspections (years): 3

3.2 Has the manufacture of this type of dosage form been inspected?

Yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization?[14]

Yes

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

No. If no, explain:

Not on all aspects because the product is not registered in The Netherlands. The manufacturing site meets current GMP.

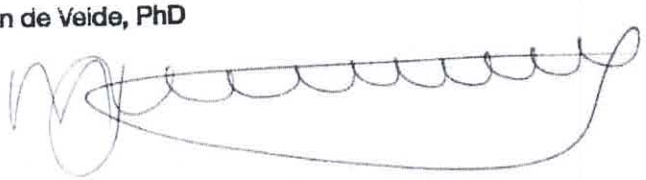
Address of certifying authority:

Ministry of Health, Welfare and Sport
CIBG
P.O. Box 16114
2500 BC Den Haag, The Netherlands
tel. : +31 70 340 6624
fax : +31 70 340 7426

Name of authorized person:

dr. M.J. van de Veide, PhD

Signature:



Stamp and date:

3 0 JUNI 2022

APOTHEEK A15

Appendix at request for Certificate of a Pharmaceutical Product

Flucytosine infusion 10 mg/ml, 250 ml bottle

Phone: 0183-820820
E-mail: c.vermaat@apotheeka15.nl
Reference: CPP appendix 1
Date: 01-06-2022

Address
Buys Ballotstraat 2
4207 HT Gorinchem

CoC: 50841769
VAT-number: NL822955635B01

Formula and use of ingredients

The formula of Flucytosine 10 mg/ml, 250 ml bottle is per bottle as follows:

Flucytosine	active ingredient		2.5 g
Trometamol	buffering agent		305 mg
Sodium chloride	isotonicity		1.85 g
Hydrochloric acid 4M	adjustment pH to 7.4		app. 0.5 ml
Water for injections	solvent	to	250 ml

- The choice of the ingredients is based on and identical to the SmPC of Ancotil® and part 1A of the marketing authorisation dossier of Ancotil®.
- The ingredients are commonly used for parenteral products and need no further justification.

Written by C. H. Vermaat, MSc.,
QA Manager and Qualified Person Apotheek A15,
1 June 2022