REPUBLIC OF TURKEY
MINISTRY OF HEALTH
TURKISH MEDICINES AND MEDICAL DEVICES AGENCY
Certificate of a Pharmaceutical Product[1]

OK

...o the format recommended by the World Health Organization
...d explanatory notes attached)

Date: 05/10/2021

Certificate No : 2021/3045

Exporting Country : TURKEY
Importing Country : North Macedonia

1. Name and dosage form of product : **TOPOTU 4mg/4ml Concentrated Solution for Infusion**

1.1. Active ingredient(s)[2] and amount(s) per unit dose :[3] : **Topotecan hydrochloride 1,0865 mg equivalent to 1mg/1ml Topotecan**

For complete qualitative composition including excipients, see attached.[4]

1.2. Is this product licensed to be placed on the market for use in the exporting country?[5] yes/no *(key in as appropriate)* : **Yes**

1.3. Is this product actually on the market in the exporting country? Yes/no/unknown *(key in as appropriate):* **Yes**

If the answer to 1.2. is yes, continue with section 2A and omit section 2B.
If the answer to 1.2. is no, omit section 2A and continue with section 2B.[6]

2A.1. Number of product licence[7] and date of issue : **2016/599-18/08/2016**

2A.2. Product-licence holder (name and address) : **Onko İlaç Sanayi ve Ticaret A.Ş.**
Gebze OSB2 Mah. 1700. Sk. No: 1703/2
Çayırova/Kocaeli/Turkey
Manufacturing Site: Onko İlaç Sanayi ve Ticaret A.Ş
GOSB 1700. Sk. No: 1703 Çayırova/Kocaeli/Turkey

2A.3. Status of product-licence holder :[8] a/b/c *(key in appropriate category as defined in note 8)* **a**

2A3.1. For categories b and c the name and address of the manufacturer producing the dosage form are :[9] (Key in appropriate category as defined in note 8)

2A.4. Is Summary Basis of Approval appended ?[10] yes/no *(key in as appropriate): No*

2A.5. Is the attached, officially approved product information complete and consonant with the licence ?[11] yes/no/not provided *(key in as appropriate): NOT PROVIDED*

2A.6. Applicant for certificate, if different from licence holder (name and address) :[12] ----------

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

2B.2. Status of applicant : a/b/c *(key in appropriate category as defined in note 8)* ----------

2B.2.1. For categories b and c the name and address of the manufacturer producing the dosage form are :[9] ----------

2B.3. Why is marketing authorization lacking? Not required/not requested/under consideration/refused (key in as appropriate) ----------

2B.4. Remarks :[13] ----------

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? yes/no/not applicable[14] *(key in as appropriate) :* **Yes**
If no or not applicable proceed to question 4.

3.1. Periodicity of routine inspections (years) : **In every 3 years.**

3.2. Has the manufacture of this type of dosage form been inspected? yes/no (key in as appropriate) : **Yes**

3.3. Do the facilities and operations conform to GMP as recommended by the World Health Organization)[15] yes/no/not applicable[14] *(key in as appropriate) :* **Yes**

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product ?[16] yes/no *(key in as appropriate):* **Yes**

If no, explain

Digitally signed by Guțan Ghenadie
Date: 2021.12.14 16:33:48 EET
Reason: MoldSign Signature
Location: Moldova

This certificate is valid until 05.10.2023

Address and certifying authority:
REPUBLIC OF TURKEY
MINISTRY OF HEALTH
TURKISH MEDICINES AND MEDICAL DEVICES AGENCY
SÖĞÜTÖZÜ MAH. 2176 SOK. NO:5 ÇANKAYA/ANKARA
FAX: (0312) 218 30 03 PHONE: (0312) 218 30 00

T.C.

Oğuzhan KAYUNCU

Name of authorized person

Oğuzhan KAYUNCU M.Sc.Pharm.
Head of Herbal and Supportive Medicines Department

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation Scheme.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

1. This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
2. Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
3. The formula (complete composition) of the dosage form should be given on the certificate or be appended.
4. Details of quantitative composition are preferred but their provision is subject to the agreement of the product-licence holder.
5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.
6. Sections 2A and 2B are mutually exclusive.
7. Indicate, when applicable, if the licence is provisional, or the product has not yet been approved.
8. Specify whether the person responsible for placing the product on the market:
   (a) manufactures the dosage form;
   (b) packages and/or labels a dosage form manufactured by an independent company; or
   (c) is involved in none of the above.
9. This information can only be provided with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence has to be updated or it is no longer valid.
10. This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
11. This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC)
12. In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission has to be provided to the authority by the applicant.
13. Please indicate the reason that the applicant has provided for not requesting registration.
   (a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;
   (b) the product has been reformulated with a view to improving its stability under tropical conditions;
   (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
   (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
   (e) any other reason, please specify.
14. Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.
15. The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).
16. This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

3.2.P.1.1 Description and Composition of the Drug Product (Topotu 4 mg/4 ml Concentrated Solution for Infusion)

Description:

A clear yellow color solution filled in an amber glass vial free from visible foreign particles. Topotu 4 mg/4 mL Concentrated Solution for Infusion is supplied in 6R (10 ml) Type I glass vials.

Composition:

Raw Material Name	Quantity in mg per mL	Function	Reference to quality standards
Topotecan Hydrochloride[1]	1,0865	Antineoplastic agent	In-house
Tartaric Acid	5,00	Acidifying agent	Ph. Eur./ USNF
Sodium Hydroxide[2]	q.s[4]	For pH adjustment	Ph. Eur./ USNF
Hydrochloric Acid 37-38 %[3]	q.s[4]	For pH adjustment	Ph. Eur./ USNF
Water for injection	q.s to 1mL	Solvent	IP & USP & Ph. Eur.
Carbondioxide	q.s[4]	Sparging in bulk solution and headspace	Ph. Eur./ USP

[1]The amount of active substance is calculated based on the moisture content. (1,0865 Topotecan Hydrochloride is equivalent to 1,0 mg Topotecan)
[2]1N NaOH is used for pH adjustment.
[3]10% HCl is used for pH adjustment.
[4]q.s: quantity of sufficient

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Tic. Sic. No: 23589 İlyasbey V.D.: 643 037 2352
Mersis No: 0643 0372 3520 0017

Hatice SAYGI
Regulatory Affairs Manager