Decentralised Procedure

RESPONSES TO DAY 70 AND DAY 100 COMMENTS

MODULE 1

Trientin Waymade 200 mg Hartkapseln
Trientine Dihydrochloride

DE/H/6991/001/DC

Applicant: Waymade B.V

Reference Member State	DE
Concerned Member States	AT, DK, EL, ES, FI, FR, IT, NL, NO, PT, SE
Start of the procedure:	12.03.2021

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I LIST OF QUESTIONS as proposed by RMS

45. The type of stearic acid should be stated in section 2.6.1 of the Application Form. This should be in line with the excipient used in the validation batches. From the CoA provided in section 3.2.P.4, stearic acid (50) is used.

Response: We noted the agency's comment and section 2.6.1 of the **eAF** has been updated to specify the type of stearic acid i.e., stearic acid (50).

46. In section, 2.6.1 of the Application Form, the qualitative and quantitative composition of Black Ink should be stated. For the ingredients, also reference should be made to the Ph. Eur where applicable, in line with the declaration of the supplier. Black iron oxide should meet the requirements of (EU) 231/2012 (E172).

Response: As suggested by the agency, section 2.6.1 of eAF has been updated to add the qualitative and quantitative composition of Black Ink. Also, references to the Ph. Eur. has been made in line with the declaration of the supplier. Moreover, as per the declaration provided in section 3.2.P.1 (sequence 0000), black iron oxide met the requirements of (EU) 231/2012 (E172).

47. According to the information in Module 3, section 3.2.P.7, the closure of the bottle is a white polypropylene screw cap with induction heat seal liner. Section 2.2.3.1 of the Application Form should be updated accordingly.

Response: As recommended by the agency, section 2.2.3.1 of the **eAF** has been updated to amend the description of the closure from "polypropylene closure" to "white polypropylene screw cap with induction heat seal liner".

48. For the finished product manufacturer Apothecon Pharmaceuticals Pvt. Ltd, the GMP Certificate issued by the MHRA (based on an inspection at 03/12/2019) is restricted to the manufacture and primary packaging of tablets and hard shell capsules in Block B. The information on the manufacturer of the drug product should be updated accordingly in section 2.5.2 of the Application Form with the statement that manufacture and primary packaging of the Trientine 200mg hard capsules is performed in Block B only.

Response: We noted the agency's comment and can confirm that manufacturing and primary packaging of the Trientine 200mg hard capsules is performed in Block B only. The information on the manufacturer of the drug product has been updated in section 2.5.2 of the **eAF** to state that manufacturing and primary packaging of the Trientine 200mg hard capsules is performed in Block B only.

SmPC and PL:

49. According to the information in Module 3, section 3.2.P.7, the bottle is closed with a white polypropylene screw cap with induction heat seal liner. Section 6.5 of the SPC and section 6 of the PIL. should be updated accordingly.

Response: As suggested by the agency, section 6.5 of the **SPC** and section 6 of the **PIL** have been updated to update the description of bottle closure from "polypropylene closure" to "white polypropylene screw cap with induction heat seal liner".

Product name

50. The proposed product name for procedure DE/H/6991/001/DC (in annex 5.19) can be accepted given that the German word Trientin (instead of Trientin**e**) is used. Therefore, please update the name in annex 5.19 to "Trientin Waymade 200 mg Hartkapseln".

Response: The **annex 5.19** has been updated to correct the product name for the Germany to "Trientin Waymade 200 mg Hartkapseln".

Assessment of User Testing

The applicant has stated that the readability test will be performed during clock stop. The RMS agrees with this.

As per the Article 59(3) of the directive 2001/83/EC, as amended "*the package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.*"

However, applicant has submitted user testing bridging proposals in accordance with the QRD guidance. Please refer the QRD form for submission and assessment of user testing bridging proposals in **section 1.3.4**.

II LIST OF QUESTIONS as proposed by CMS (Day 100: DK)

Other concerns

Module I – Application

Name
The product name Trientine Waymade is not considered acceptable in DK pt. for the following reason(s):
Please change to Trientin "Waymade" in line with the Danish wording (without "-e")

Responses: As suggested by the agency, the product name in the DK has been updated as below. **Annex 5.19** has been updated accordingly.

Current product name	Proposed product name
Trientine Waymade 200 mg hårde kapsler	Trientin Waymade 200 mg hårde kapsler

Legal status
The applicant has applied for the legal status "Product on prescription which may be renewed". In Denmark, the legal status will be "Product on restricted prescription" in line with the legal status for the orginator Cufence. The application form should be updated accordingly.

Responses: We noted the agency's comment and the **eAF** section 2.3.2 has been updated to correct the legal status from "Product on prescription which may be renewed" to "Product on restricted prescription".

III LIST OF QUESTIONS as proposed by CMS (Day 100: FR)

Other concerns not already raised by the RMS

SmPC

Other concerns not already raised by the RMS

4.1 The indication treatment of gall reflux gastritis should be deleted as it is not authorised in France.

Responses: We noted the agency's comment and would like to clarify that proposed product is not indicated for gall reflux gastritis. The proposed product is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older. The proposed indication is in line with the reference product Cufence 200 mg hard capsules.

6.1 List of excipients

The E numbers should be given when the excipient is listed in the Guideline on the excipients in the label and package leaflet of medicinal products for human use as having recognised action or effect.

Capsule content:
Stearic acid

Capsule shell:
Gelatin
Titanium dioxide (E171)

Printing ink:
Shellac ~~(E904)~~
Propylene Glycol ~~(E1520)~~
Black Iron Oxide (E172)
Potassium Hydroxide ~~(E525)~~

Responses: As suggested by the agency, SmPC section 6.1 has been updated to mentions the E numbers only for the excipients listed in the Guideline on the excipients in the label and package leaflet of medicinal products for human use as having recognised action or effect.

PL

Please note that the name authorised in France is
TRIENTINE WAYMADE 200 mg, gélule
Please add: Trientine Dihydrochloride

Response: We noted the agency's comment and would like to clarify that the proposed product name in the France is "Trientine Waymade 200 mg gélule". The same product name is already provided in Annex 5.19 submitted in sequence 0001.

However, as suggested by the CMS, the title of the PL has been updated to mention "trientine dihydrochloride" in place of "trientine".

5. HOW TO STORE X

6. FURTHER INFORMATION

What Trientine Waymade capsules contain
The active substance is trientine.
Each hard capsule contains 300 mg trientine dihydrochloride, equivalent to 200 mg trientine.

The other ingredients are
Capsule content: Stearic acid
Capsule shell: Gelatin, titanium dioxide (E171)
Printing ink: Shellac ~~(E904)~~, propylene glycol ~~(E1520)~~, black iron oxide (E172), potassium hydroxide ~~(E525)~~

What Trientine Waymade capsules look like and contents of the pack
Each hard capsule is a cylindrical size "1" hard gelatin capsule with an opaque, white coloured-cap, printed with "Waymade" in black ink and an opaque white coloured body, printed with "Trientine 300 mg" in black ink. The capsule is filled with white to off-white powder.
White, high density polyethylene (HDPE) round bottles, containing a silica gel desiccant in the bottle, and closed with a polypropylene closure.
Pack size: A bottle of 100 hard capsules in a carton.

Responses: We noted the agency's comment and section 6 of the PL has been amended as suggested by the agency.

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

{Carton and Bottle}

1. NAME OF THE MEDICINAL PRODUCT

Please note that the name authorised in France is
TRIENTINE WAYMADE 200 mg, gélule
Please add: Trientine Dihydrochloride

Responses: We noted the agency's comment and would like to clarify that the proposed product name in the France is "Trientine Waymade 200 mg gélule". The same product name is already provided in Annex 5.19 submitted in sequence 0001.

We noted the agency's comment and labelling text for carton and bottle are updated in include "trientine dihydrochloride".

Module I – Application related comments (including product name)

- [redacted]

Responses: [redacted]

- [redacted]

Responses: [redacted]

NAME OF THE MEDICINAL PRODUCT

Please note that the name authorised in France is
TRIENTINE WAYMADE 200 mg, gélule

Responses: We noted the agency's comment and would like to clarify that the proposed product name in the France is "Trientine Waymade 200 mg gélule". The same product name is already provided in Annex 5.19 submitted in sequence 0001.

IV LIST OF QUESTIONS as proposed by CMS (Day 100: SE)

Other concerns not already raised by the RMS

SmPC

Section 2
It should be read "Each hard capsule contains 300 mg trientine dihydrochloride equivalent to 200 mg trientine".

Responses: We noted the agency's comment and would like to clarify that section 2 of the SmPC already contain the statement "Each hard capsule contains 300 mg trientine dihydrochloride equivalent to 200 mg trientine".

Section 3
The size (mm) of the capsule should be given instead of size 1.
This should be deleted "~~The capsule filled with white to off-white powder~~"

Response: As suggested by the agency, the dimension of the capsule i.e., lock length - 19.30 ± 0.40 mm has been added in section 3 of the SmPC. Moreover the statement "The capsule filled with white to off-white powder" has been removed.

Section 4.2
It should be clarified whether the whole capsule can be taken for an empty stomach

Response: We noted the agency's comment and would like to clarify that information related to use of trientine capsule with empty stomach is already included in the SmPC section 4.2 as below. This is in line with the SmPC of reference product; Cufence 200 mg hard capsules.

"*It is important that Trientine Waymade capsules are given on an empty stomach, at least one hour before meals or two hours after meals, and at least one hour apart from any other medicinal product, food or milk (see section 4.5).*"

Section
Section 4.4
The following statement is not included in the SmPC for the centrally approved product Cufence. The statement is also contradictory to the indication (treatment of patients intolerant to D-Penicillamine therapy). Please delete:
~~There is no advantage in using trientine and penicillamine in combination.~~

Response: The SmPC section 4.4 has been updated as suggested by the agency.

Section 6.1
The Swedish Medical Products Agency considers that E-numbers of excipients may be valuable information for patients. The applicant is thus, on a voluntary basis, asked to include all available E-numbers in section 6.1.

Response: We noted the agency's comment and would like to clarify that section 6.1 of the SmPC has been updated as per CMS comments from FR.

V LIST OF QUESTIONS as proposed by CMS (Day 100: AT, ES, FI, IT, NL, NO)

Module 1
No Day 100 comments on Module 1 part.

VI Additional information

In addition to above changes, we applicant wished to update following information along with this response.

1. Update in PSMF:

The section 1.8.1 has been updated to include the updated EU Summary of the Pharmacovigilance System. The summary of the pharmacovigilance system was revised for update in QPPV details. The section 2.4.4 of the **eAF** has also been updated accordingly.

2. Change in contact person:

We wish to change the person authorised for communication on behalf of the applicant during/after the procedure. The present vs proposed change in contact person detail is summarised in following table. The declaration part and section 2.4.2 of the **eAF** are updated accordingly whereas the letter of authorisation has been provided as **Annex 5.4** in section 1.2.

Present	Proposed
[redacted]	Title: Ms. First name: Margi Surname: Shah Company name: Waymade Plc Address: Sovereign House, Miles Gray Road, City/Locality/Town/Village: Basildon County: Essex Postcode: SS14 3FR Country: UK Telephone: [redacted] E-mail: margi.shah@waymade.co.uk

3. Exploitant in FR:

In France, we propose MEDIPHA SANTE as Exploitant of this product. The declaration has been provided under additional data in Module 1.

4. Removal of "Propylene Glycol (E1520)" from section 6.1 of the SmPC and section 6 of the PIL:

We would like to clarify that as per the "*GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS*", ingredients of the printing ink that evaporates during the process and not present in the final product should not be included in the Section 6.1 of the SmPC. As per the following supplier's declaration, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution and purified water gets evaporated completely after printing & drying process. Hence, section 6.1 of the SmPC and section 6 of the PIL are updated to remove the propylene glycol. The ingredients remaining on capsules after printing (shellac, black iron oxide and potassium hydroxides) are mentioned in the SmPC and PIL.

July 17, 2020

Rev. No.	03
Effective Date	17-07-2020
Valid Upto	17-07-2023

TO WHOMSOEVER IT MAY CONCERN

With reference to your query regarding ingredients of the printing ink that evaporates during imprinting, please find below reply.

All solvents used in TekPrint™ SW-9008 Black Ink that is Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution & Purified Water gets evaporated completely after printing & drying process.

Only ingredient remaining on capsules after printing is shellac, Black Iron Oxide & trace amount (less than 1 ppb) of Potassium salts of potassium hydroxides.

Declaration is based on Information received from ink vendors.

Regards,

[redacted]

Asst. Executive- Global Regulatory Affairs

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CIN No. : U24239MH1961PTC012061 I GST No. : 27AAACA4769K1ZD