COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cytomel 5 and 12.5 micrograms, tablets

(liothyronine sodium)

NL Licence RVG 121883-121884

Date: 8 January 2020

This module reflects the scientific discussion for the approval of Cytomel 5 and 12.5 micrograms, tablets. The marketing authorisation was granted on 18 October 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Cytomel 5 and 12.5 micrograms, tablets from ACE Pharmaceuticals B.V.

The product is indicated in the treatment of hypothyroidism in addition to levothyroxine treatment. Cytomel is indicated in nontoxic goiter. Cytomel is also used as part of the diagnostic T3 suppression test.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a line extension of Cytomel 25 microgram tablets (NL Licence RVG 108769), which was authorised in the Netherlands on 12 November 2010. Cytomel 25 microgram tablets are cross scored and can be divided into quarters, which enables a dosage of 12.5 or 6.25 micrograms. However, issues concerning the breakability in quarters have been reported. Therefore Cytomel 5 and 12.5 micrograms tablets were developed. Both bear a score line. The two lower strengths have been available as named patient product since 2013 (12.5 mcg) and since 2015 (5 mcg).

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

The active substance of Cytomel is considered well-known. Reference is made to information contained in the pharmacological-toxicological, non-clinical and clinical part of the dossier of the authorisation of the previous Cytomel authorisation. Reference to the non-clinical and clinical studies performed with Cytomel 25 microgram tablets is acceptable for this line extension. The MEB agreed that additional studies are not required.

II. QUALITY ASPECTS

II.1 Introduction

Cytomel 5 and 12.5 micrograms are white, round, biconvex tablets with a bisect breakline on one side to break them into equal halves. The other side has the inscription “CYTOMEL 5” or “CYTOMEL 12.5”. The tablets contain respectively 5.17 and 12.92 micrograms of liothyronine sodium, corresponding to 5 and 12.5 micrograms liothyronine.

The tablets packed in Al/Al blisters.

The excipients are gelatin (E441), croscarmellose sodium (E468), calcium sulfate dihydrate and magnesium stearate (E470b).

The two tablet strengths are not dose proportional.

II.2 Drug Substance

The active substance is liothyronine sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or slightly coloured hygroscopic powder, which is practically insoluble in water and slightly soluble in 96% ethanol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. with additional requirements for ethylamine and ethanol. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full-scale batch. Since additional batch data has been reviewed by the EDQM as part of the CEP application, this is acceptable.

Stability of drug substance
The active substance is stable for 12 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The current products are line extensions of the already marketed 25 micrograms Cytomel strength. The development focused on breakability of the tablets and comparative dissolution characteristics compared to the higher strength. No clinical/bioequivalence studies were performed.
The functionality of the score line has been tested in accordance with the general Ph. Eur. monograph on tablets. Breakability of two batches of both strengths has been tested. The results of all batches complied with the specifications and are included in the dossier. The

hardness of the tablets is adequate to break them into equal halves to provide a dosing of 2.5 mcg (5 mcg tablet) or 6.25 mcg (12.5 mcg tablets).
Comparative dissolution data of both the 5 and the 12.5 microgram strengths versus the 25 microgram strength were determined. All strengths show rapid dissolution (>85% in 15 min.) at all pHs (i.e. 1.2, 4.5, 6.8), except for the 25 microgram strength, which shows variable results at 15 minutes, with mean result >85% for one batch and a mean result of 80.3% for a second batch. As also analytical variability is seen, due to the low amounts of active substance, the dissolution profiles of all strengths can be considered similar. The pharmaceutical development of the products has been adequately performed.

Manufacturing process
The tablets are manufactured by means of wet granulation. The active substance is dissolved in ethanol before adding it to a granulate of calcium sulfate and gelatin. The other excipients are subsequently added and mixed. The obtained granulate is tabletted and packed. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for four commercial-scale batches of the 5 microgram strength and three full-scale batches of the 12.5 microgram strength.

Control of excipients
The excipients comply with the Ph. Eur. specifications. Adequate limits have been defined for the functionality related characteristics. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, resistance to crushing, dissolution, related substances, uniformity of dosage units, assay and microbiological quality. Separate release and shelf-life limits have been defined for assay, related substances and resistance to crushing. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on four commercial-scale batches of the 5 mcg strength and two full-scale batches of the 12.5 mcg strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for four batches of the 5 microgram strength and five batches of the 12.5 microgram strength. Of the five batches of the 12.5 microgram strength only two were packed in the proposed primary packaging material (Al/Al blister); the other three were packed in a less protective package (PVC-PVDC/Al blister). Hence the additional three batches are seen as supportive data. The batches were stored at 5°C ± 3°C (up to 24 months for the 5 microgram strength and 36 months for the 12.5 microgram strength) and 25°C/60% RH (up to 24 months for the 5 microgram strength and 18 months for the 12.5 microgram strength). The conditions used in the stability studies are according to the ICH stability guideline.
Under both storage conditions a decrease in assay and an increase in impurities is seen. Although the assay results show analytical variability, the long-term data show that no out-

of-specification results have been observed up to 24 months. Therefore the shelf-life of 24 months is acceptable, with the storage condition “store in the refrigerator (2-8°C)”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A BSE/TSE statement for the used gelatin has been provided. The used gelatin is of porcine origin, and there is no TSE risk for this gelatin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Cytomel 5 and 12.5 micrograms, tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to submit a variation to replace the score cross on the 25 mcg tablet with a score line within 3 months of the national authorisation of the 5 mcg and 12.5 mcg strengths.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Cytomel 5 mcg and Cytomel 12.5 mcg tablets will be prescribed for the same indication as Cytomel 25 mcg tablets. The MAH stated that patients will obtain a dosage more appropriate to their specific situation, which will not be higher than currently obtained with Cytomel 25 mcg tablets. It is not expected that more patients will use the product. Therefore, the approval of the additional strengths will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a line extension to Cytomel 25 mcg, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the 25 mcg application. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The MAH argued that no *in-vivo* bioavailability studies were necessary since liothyronine sodium is a highly soluble drug substance. No bioequivalence study has been performed and a waiver for the two additional strengths was applied for.

Comparative dissolution data of the 5 and the 12.5 microgram strength versus the 25 microgram strength were determined. All strengths show rapid dissolution (>85% in 15 min.) at all pHs (i.e. 1.2, 4.5, 6.8), except for the 25 microgram strength, which shows variable results at 15 min.

Due to the rapid dissolution of most batches and the high standard deviation at early time points, no f2 value can be calculated to compare the dissolution profiles. It has been demonstrated that high analytical variability is hampering the accurate determination of amounts dissolved. Overall, the dissolution profiles of all strengths can be considered similar. The batch-to-batch consistency for the 5 and 12.5 microgram strengths is ensured by the dissolution specification, which has been tightened to NLT 85% (Q) at 15 minutes. Finally, it can be seen that at the lower pH values dissolution is very rapid. Therefore, it is expected that all active substance will have dissolved in the stomach before reaching the intestines, and no effect on the clinical efficacy is foreseen.

IV.2 Risk Management Plan

The MAH submitted a statement on the absence of a Risk Management Plan. This application concerns a line extension of an active ingredient with a well-known safety profile that has been in use for many years. There is currently no RMP for Cytomel 25 mcg tablets and no new safety issues related to the line-extension are anticipated.
The MEB agrees that, in line with Good Pharmacovigilance Practices (GVP), no RMP is required in the context of this line extension application and that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for Cytomel.

IV.3 Discussion on the clinical aspects

For this line extension authorisation, reference is made to the clinical dossier of Cytomel 25 mcg. Liothyronine sodium is a well-known active substance with established efficacy and tolerability. The MEB agreed that no new clinical studies were conducted. A biowaiver for the two lower strengths has been granted, as adequate dissolution data demonstrating similarity have been provided. Risk management is sufficiently addressed.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. Reference is made to the PL for Cytomel 25 mcg. Cytomel 5 mcg and 12.5 mcg tablets will be prescribed for the same indication as Cytomel 25 mcg tablets. Besides the insertion of the additional strengths and the minimal dose of 2.5 instead of 6.25 micrograms, no other texts will be changed in the PL. The MEB agreed that user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cytomel 5 and 12.5 micrograms, tablets have a proven chemical-pharmaceutical quality and are a legitimate line extension to Cytomel 25 mcg tablets. Cytomel is a well-known medicinal product with an established favourable efficacy and safety profile.

A bioequivalence study of the 5 mcg and 12.5 mcg strengths versus the 25 mcg strength was not required, as all conditions for granting a biowaiver have been met. Similarity of dissolution profiles has been adequately demonstrated.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, has granted a marketing authorisation. Cytomel 5 and 12.5 micrograms, tablets were authorised in the Netherlands on 18 October 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse