

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Clemastine TioFarma 1 mg, tablets
TioFarma b.v., the Netherlands**

clemastine (as fumarate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.

It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 106795

13 November 2013

Pharmacotherapeutic group:	antihistamines for systemic use
ATC code:	R06AA04
Route of administration:	oral
Therapeutic indication:	prevention and symptomatic treatment of allergic conditions induced by histamine,
Prescription status:	prescription only
Date of authorisation in NL:	16 January 2013
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Clemastine TioFarma 1 mg, tablets from TioFarma b.v. The date of authorisation was on 16 January 2013 in the Netherlands.

The product is indicated for:

- prevention and symptomatic treatment of allergic conditions induced by histamine, such as hay fever and perennial rhinitis, urticaria and other dermatoses based on allergies of the direct type (e.g. prurigo, insect-bites), drug-induced exanthema and as adjuvant therapy in other cases of eczema.
- prophylactic against allergy based side-effects during hyposensibilisation therapy.
- adjuvant therapy in cases of allergic asthma.

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

Clemastine belongs to the class of ethanolamine derivative antihistamines which belongs to the first generation of H1 receptor antagonists. Clemastine is an inverse agonist of histamine, which means that it binds to the same receptor as histamine and thus exerts an opposite effect by preventing histamine actions on the peripheral tissues. Histamine H1 receptors are expressed throughout the body, specifically in smooth muscles, on vascular endothelial cells, in the heart, and in the central nervous system. Like other first-generation H1-antihistamines, clemastine passes the blood-brain barrier and affects CNS functions.

This national procedure concerns a generic application claiming essential similarity with the innovator product Tavegyl 1 mg tablets (NL License RVG 05621), which has been registered by Novartis Consumer Health B.V. since 13 November 1968.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Tavegyl 1 mg tablets as registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is clemastine fumarate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is very slightly soluble in water.

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 European Pharmacopoeia.

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 CEP. Certificates of analysis for three batches have been provided. The results comply with the specification laid down.

Stability of drug substance

Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (4 years). The re-test period and packaging material have not been stated on the CEP and could not be granted based on the provided data. The MAH confirmed that the active substance will be tested for compliance with the Ph.Eur. and CEP requirements immediately prior to use.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Clemastine TioFarma 1 mg is a white to off white, flat bevelled edged tablet with score on one side and the inscription 'Clemastine 1' on the other side.

The tablets contain 1.34 mg clemastine fumarate which corresponds to 1 mg clemastine.

The tablets are packed in in PVC/Aluminium blisters or white PP containers provided with LDPE snap secure closure.

The excipients are: are silicified microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, talc and magnesium stearate.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The pharmaceutical development of the product was initially incomplete. A waiver for

bioequivalence study was requested. However, high solubility of clemastine and similarly rapid dissolution of the test and reference product *i.e.* > 85% within 30 min dissolved at the entire pH range of 1-6.8 were not demonstrated. Therefore, these criteria for a waiver of bioequivalence study, as outlined in Guideline on the investigation of bioequivalence CHMP/EWP/QWP/1401/98 Rev. 1, Annex 3, were not met and a comparative bioavailability study is necessary to demonstrate equivalence between Clemastine TioFarma 1 mg tablets and Tavegyl 1 mg tablets. Therefore the MAH provided a bioequivalence study. The study was performed with the Dutch reference product.

Breakability of the tablets is not tested, as the dosage regime in the SPC does not prescribe administration of half tablets. The score line is only present for cosmetic reasons, which is stated in the SPC.

Manufacturing process

A dry powder mixture is prepared and tablets are obtained by direct compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full-scale batches. In view of the low active substance content the manufacture is considered 'non-standard'. The MAH revised the validation protocol based on comments by the MEB. The process is considered sufficiently controlled.

Control of excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, mean weight, uniformity of mass, mean weight half tablet, uniformity of mass half tablet, disintegration, identification fumaric acid, identification clemastine, assay, uniformity of dosage units, water content, dissolution rate, related substances, hardness, friability and microbiological purity.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided 3 full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in blister packaging or containers. At long-term conditions the assay results show fluctuation. There is no clear trend in assay decrease observed. The results on the related substance testing do not show any trends either.

At accelerated conditions significant decrease in assay, increase in impurities, decrease in dissolution rate, decrease in hardness are observed in both the tablets stored in the blister packaging and the container. No results of intermediate stability studies were provided.

Based on the long-term data, a shelf-life of 2 years was granted, when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A statement on the availability of a Ph.Eur. Certificate of suitability for TSE for the lactose used has been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Tavegyl which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of clemastine released into the environment. It

does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Clemastine is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH initially applied for a biowaiver based on a BCS Class 1 classification for the product. This was not sufficiently justified. Therefore the MAH submitted a bioequivalence study in which the pharmacokinetic profile of the test product Clemastine TioFarma 1 mg (TioFarma b.v., the Netherlands) is compared with the pharmacokinetic profile of the reference product Tavegyl 1 mg tablets (Novartis Consumer Health B.V., the Netherlands).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, with mean age 27.6 years. Each subject received a single dose (1 mg) of one of the 2 clemastine formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00 and 72.00 hours after administration of the products.

The study design is considered appropriate. The washout period of at least 14 days was sufficient to ensure complete elimination of the drug.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Five subjects did not report to facility for period 2 check-in and hence were considered as dropouts. The pharmacokinetic and statistical analysis was performed on the 37 subjects who completed the study.

Table 1. Pharmacokinetic parameters (un-transformed values; arithmetic mean \pm SD, t_{\max} (median (range))) of clemastine under fasted conditions.

Treatment N=37	AUC _{0-72h} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	21.7 \pm 15.8	0.895 \pm 0.381	6.00 (2.00-8.00)	21.5 \pm 6.9
Reference	20.3 \pm 14.2	0.854 \pm 0.368	6.00 (2.00-8.00)	21.1 \pm 5.8

*Ratio (90% CI)	1.05 (0.98 – 1.13)	1.06 (0.99 – 1.13)	--	--
*Intra-subject CV (%)	18.6	17.3	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life CI confidence interval CV coefficient of variance				

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of clemastine under fasted conditions, it can be concluded that Clemastine TioFarma 1 mg and Tavegyl 1 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Clemastine may be taken without reference to food intake, although it is preferably taken before meals. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Clemastine was first approved in 1968, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of clemastine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SmPC

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Tavegyl.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. Several adjustments were made to the PL prior to the pilot test, as well as before and after the first round. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both test rounds all questions were answered correctly by all of the participants. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clemastine TioFarma 1 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Tavegyl 1 mg tablets. Tavegyl is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

In the Board meeting of 28 July 2011, the application was discussed, particularly the necessity of a bioequivalence study.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Clemastine TioFarma 1 mg, tablets was authorised in the Netherlands on 16 January 2013.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CNS	Central Nervous System
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NfG	Note for Guidance
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/non approval	Assessment report attached