Public Assessment Report

UK National Procedure

Tyvera 50 mg Tablets

Thiamine Hydrochloride 50 mg Tablets

PL 17507/0056

Tyvera 100 mg Tablets

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PL 17507/0057

Auden Mckenzie (Pharma Division) Ltd

LAY SUMMARY

Tyvera 50 mg Tablets/Thiamine Hydrochloride 50 mg Tablets
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This is a summary of the public assessment report (PAR) for Tyvera 50 mg Tablets/Thiamine Hydrochloride 50 mg Tablets and Tyvera 100 mg Tablets/Thiamine Hydrochloride 100 mg Tablets. These medicinal products will be collectively referred to as Thiamine Hydrochloride Tablets in the remainder of this summary.

This summary explains how Thiamine Hydrochloride Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Thiamine Hydrochloride Tablets.

For practical information about using Thiamine Hydrochloride Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Thiamine Hydrochloride Tablets and what are they used for?
Thiamine Hydrochloride Tablets are medicines with 'well-established use'. This means that the medicinal use of the thiamine hydrochloride has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Thiamine Hydrochloride Tablets are given to patients lacking thiamine (Vitamin B1).

How do Thiamine Hydrochloride Tablets work?
Although thiamine occurs naturally in nearly all living tissues, and some is obtained from almost all foods - particularly yeast, wholegrain cereals, meat and beans - unpleasant physical symptoms can develop in patients who do not get enough thiamine in their diet. Taking Thiamine Hydrochloride Tablets - a synthetic version of natural Vitamin B1 - helps to make up for any lack of thiamine in the diet.

How are Thiamine Hydrochloride Tablets used?
The tablets should be swallowed whole with water. If patients find that a whole tablet too big to swallow, it can be broken first along the score line.

Patients taking the 50 mg tablets should take one tablet a day if they have mild chronic thiamine deficiency and two tablets three times a day if they have severe thiamine deficiency.
Patients taking the 100 mg tablets should take one tablet three times a day if they have severe thiamine deficiency. Thiamine Hydrochloride Tablets are not recommended for children under 3 years of age.

These medicines can only be obtained from pharmacies.

What benefits of Thiamine Hydrochloride Tablets have been shown in studies?
As thiamine hydrochloride is a well-known substance and its use in the authorised indications is well established, the applicant has presented data from the scientific literature. The literature provided confirmed the efficacy and safety of thiamine hydrochloride for use in the authorised indications.

What are the possible side effects of Thiamine Hydrochloride Tablets?
For the full list of all side effects reported with Thiamine Hydrochloride Tablets see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Thiamine Hydrochloride Tablets approved?
It was concluded that, in accordance with EU requirements, the benefits of Thiamine Hydrochloride Tablets outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Thiamine Hydrochloride Tablets?
Suitable safety information has been included in the Summaries of Product Characteristics and the package leaflets for Thiamine Hydrochloride Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Thiamine Hydrochloride Tablets
The Marketing Authorisations for Thiamine Hydrochloride Tablets were granted on 21 March 2007.

The full PAR for Thiamine Hydrochloride Tablets follows this summary.

For more information about treatment with Thiamine Hydrochloride Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in December 2015.

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I Introduction

Based on the review of the data on quality, safety and efficacy the UK granted Marketing Authorisations for the medicinal products Tyvera 50 mg and 100 mg Tablets to Auden McKenzie Limited (PL 17507/0056-0057) on 21st March 2007. The products are Pharmacy (P) medicines for the treatment of thiamine deficiency.

The applications were submitted as abridged applications according to Article 10a of Directive 2001/83/EC, bibliographic applications claiming a well-established use with acceptable levels of safety and efficacy for thiamine.

These tablets contain the active ingredient thiamine hydrochloride (Vitamin B_1) and are used as a synthetic version of Vitamin B_1 in people with a deficiency in their diet.

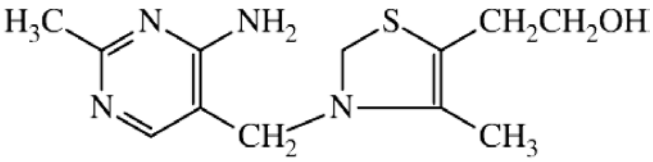
II Quality aspects

Active Substance

INN/Ph.Eur name: Thiamine hydrochloride

Chemical name: 3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride

Structural formula:



Molecular formula: $C_{12}H_{18}N_4OS$, HCl

Molecular weight: 337.3

CAS number: 67-03-8

Thiamine hydrochloride is a white or almost white crystalline powder with slight characteristic odour and bitter taste. It is freely soluble in water, slightly soluble in alcohol, soluble in glycerol, insoluble in ether and in benzene. The pH of a 2.5% solution is in the range of 2.7 to 3.3. Thiamine hydrochloride absorbs about 4% moisture on exposure to air.

Thiamine hydrochloride is the subject of a European Pharmacopoeial monograph.

The synthesis and quality of the active substance thiamine hydrochloride is controlled by a certificate of suitability.

A suitable active substance specification has been provided for thiamine hydrochloride, which is consistent with the monograph and certificate of suitability. Batch analysis data have been provided showing compliance with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 24 months when stored in the aluminium bags contained in a cardboard carton, which is the proposed container-closure. This is acceptable.

Other Ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, maize starch, sucrose, talc, sodium starch glycolate and magnesium stearate. All excipients are controlled according to their European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

With the exception of lactose monohydrate, none of the other ingredients use materials of animal or human origin in their production. A statement has been provided that lactose monohydrate used in the manufacture of the finished product is sourced from healthy animals under the same conditions as milk for human consumption and is produced using calf rennet.

Pharmaceutical development
The composition and manufacturing process for these products are based on existing formulations of thiamine hydrochloride developed by the finished product manufacturer.

Thiamine hydrochloride requires protection from light and should not be stored in metal containers.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided that comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
Both strengths of tablet are packaged in white high-density polyethylene bottles with tamper-evident peel-off seals and high-density polyethylene closures. The pack sizes for both strengths are 100 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

Stability of the product
Stability studies were performed on batches of both strengths of finished product in the packaging proposed for marketing, in accordance with current guidelines.

The data supported a shelf-life of 2 years with the storage conditions “Store in original packaging” and “Do not store above 25 degrees”.

The applicant has provided suitable post approval stability commitments.

SmPC, PIL, Labels

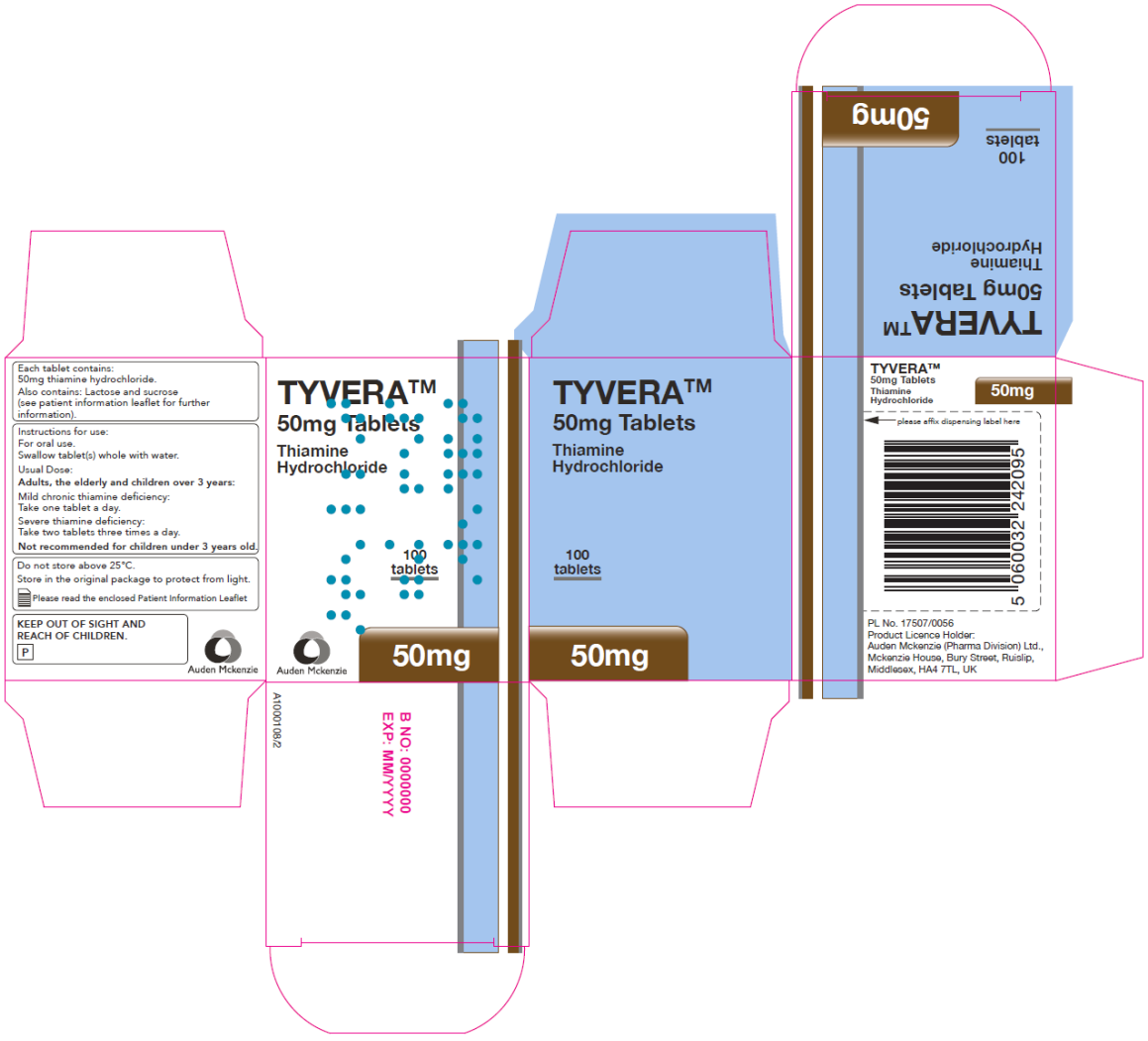
The SmPC, PIL and labelling are pharmaceutically acceptable.

The following product labelling is approved for these medicinal products:

Tyvera 50 mg Tablets

Label:

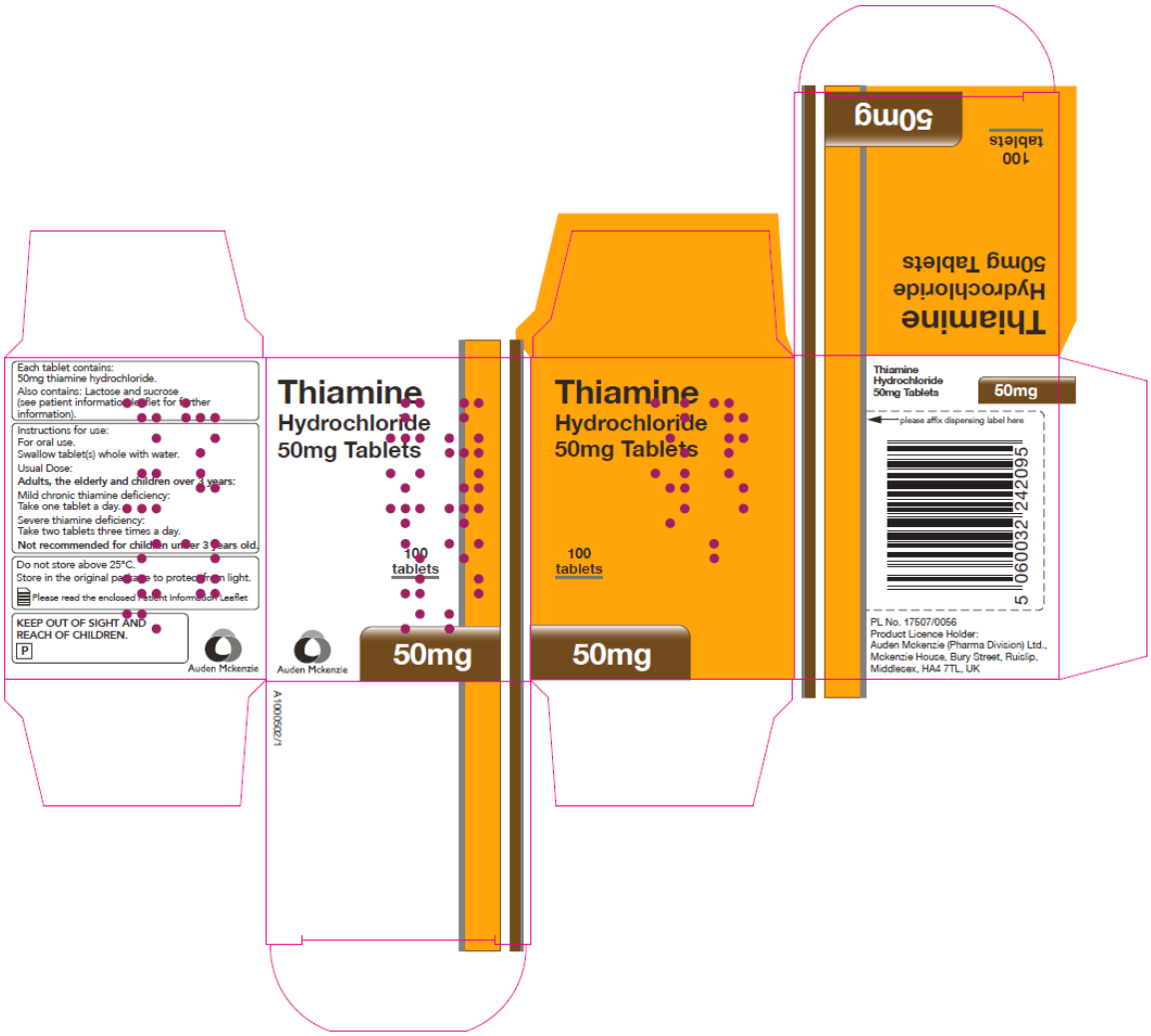
Carton:



Thiamine Hydrochloride 50 mg Tablets

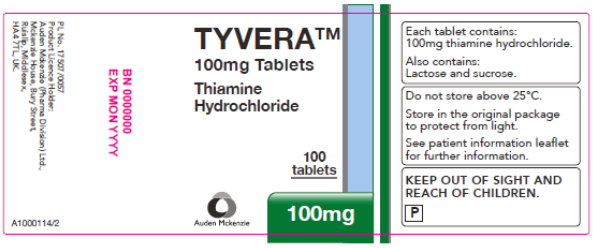
Label:

Carton:

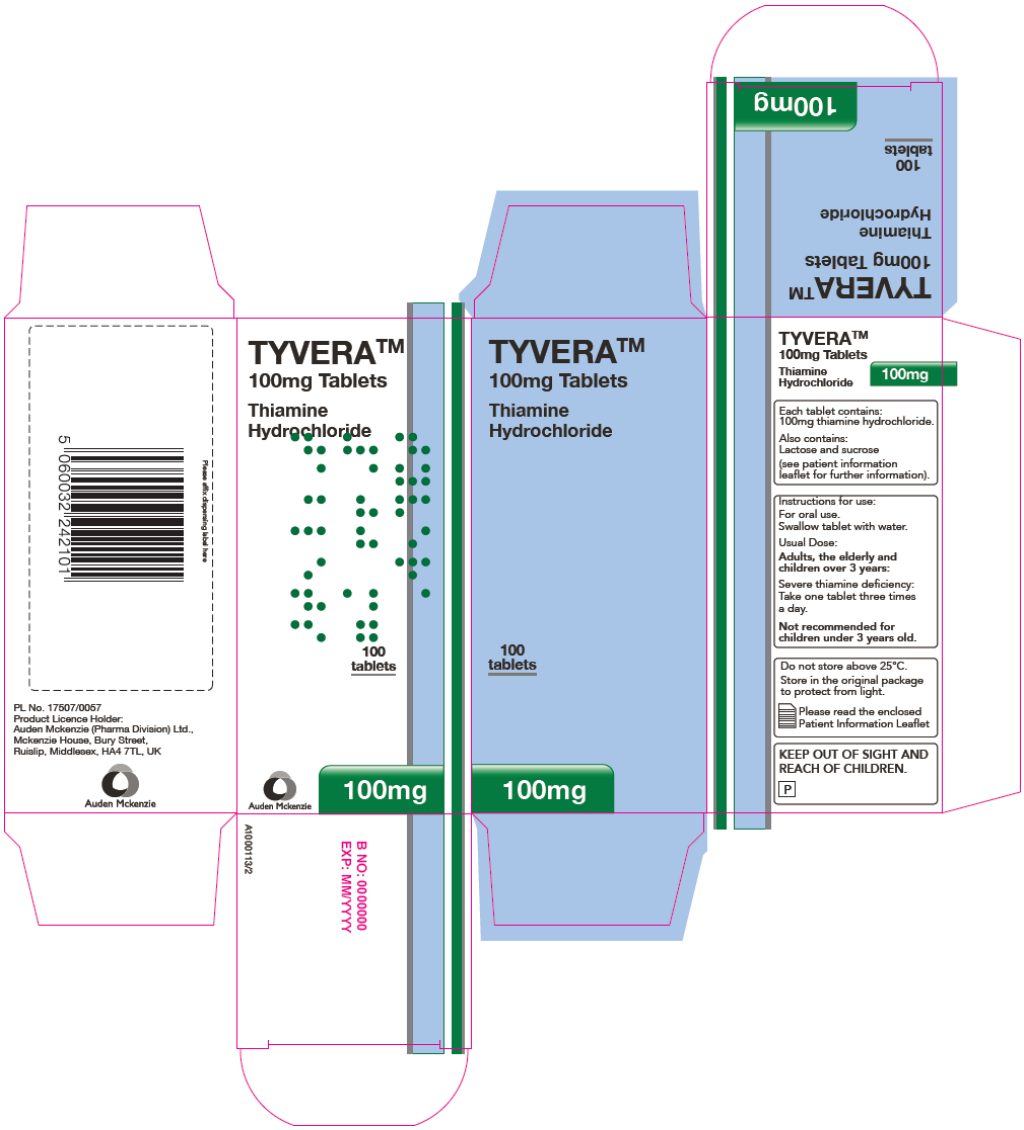


Tyvera 100 mg Tablets

Label:



Carton:



Thiamine Hydrochloride 100 mg Tablets

Label:

Carton:

Discussion on the quality aspects
The grant of Marketing Authorisations is recommended.

III Non-clinical aspects

III.1 Introduction
No new non-clinical data have been submitted and none are required. The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV Clinical aspects

Clinical pharmacology

Pharmacodynamics
Thiamine is practically devoid of discernible pharmacodynamic actions when given in usual therapeutic doses.

Pharmacokinetics
Thiamine is absorbed from the gastrointestinal tract and widely distributed to most body tissues. It is not stored in the body and amounts in excess of the body's requirements are excreted in the urine as unchanged thiamine or metabolites.

A BCS-based biowaiver has been submitted for these Marketing Authorisations. This is discussed further on page 14 of this report. has

Efficacy
The applicant has provided a satisfactory review of clinical data published in the literature confirming the efficacy of thiamine hydrochloride.

Safety
The applicant has provided an adequate review regarding the safety of thiamine hydrochloride. No new safety issues have been identified.

Expert report
A clinical expert report is provided, written by an appropriately qualified Doctor.

Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V User consultation

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, as amended.

The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

Quality
The important quality characteristics of Tyvera 50mg and 100mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-clinical
No new non-clinical data were submitted and none are required for applications of this type.

Clinical
Extensive clinical experience with thiamine hydrochloride is considered to have demonstrated the therapeutic value of the compound.

No new or unexpected safety concerns arise from these applications.

The SmPC, PIL and labelling are satisfactory.

Benefit risk assessment
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with thiamine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

VII Steps taken after initial authorisation

The following steps were taken after the initial procedure. The assessment report for the Type II variation is provided below.

Date submitted	Application type	Scope	Outcome
16/07/2007	Type 1B variation	To replace the product names Thiamine Hydrochloride 50mg Tablets and Thiamine Hydrochloride 100mg Tablets with Tyvera 50 mg Tablets and Tyvera 100 mg Tablets, respectively.	Approved - 27/09/2007
27/07/2011	Type 1B variation	To update the shelf-life of the product to 3 years in Section 6.3 of the SmPCs.	Approved - 08/09/2011
27/08/2014	Type 1B variation	To update sections 4.3, 4.4, 4.5, 4.6, 4.7 and 4.8 of the SmPCs in line with the Innovator product (Benerva).	Approved - 09/03/2015
18/09/2014	Type 1B variation	To add Thiamine Hydrochloride 50mg Tablets/Thiamine Hydrochloride 100mg Tablets) as additional names of the products; section 1 of the SmPC, the product labelling and the package	Approved - 24/10/2014

		leaflets have been updated.	
17/09/2015	Type II variation	To provide details of a biowaiver justification.	Approved - 23/11/2015

VARIATION ASSESSMENT REPORT

Reason:
To provide details of a biowaiver justification

Supporting Evidence
The initial Marketing Authorisation Applications for these medicinal products included a bioavailability study comparing the 100 mg strength tablets with similar preparations. The site where this study took place was found not to be in compliance with Good Clinical Practice and, in line with Committee for Medicinal Products for Human Use (CHMP) recommendations, the MHRA considered that data derived from this site could not be considered supportive of Marketing Authorisations.

The Marketing Authorisation Holder proposes that although the results of the initial bioavailability study should be disregarded in light of CHMP's decision, a new bioavailability study is not required as these medicinal products meet the following general requirements stipulated in the CHMP guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

1. The drug substance has been proven to exhibit high solubility (BCS class I or III) and limited absoption according to section III of the guideline
2. The very rapid *in vitro* dissolution characteristics of the test and reference products have been demonstrated considering specific requirements according to Section IV of the guideline
3. Excipients that might affect bioavailability are qualitatively and quantitatively the same.

Quality data are provided which demonstrate these criteria are met.

Evaluation
The evidence provided is adequate to prove that a BCS based biowaiver is appropriate in this case. The active substance and formulation clearly match the requirements for a BCS class III product.

Conclusion
Given that the formulations are appropriate for a biowaiver, the variation is approvable.

Decision - Approved