

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

**Temozolomide Ratiopharm 5/20/100/140/180/250 mg capsules,
hard
Ratiopharm Nederland B.V., the Netherlands**

temozolomide

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 and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

**EU-procedure number: NL/H/1665/001- 006/DC
Registration number in the Netherlands: RVG 104502,10451-4**

2 August 2010

Pharmacotherapeutic group:	antineoplastic agents and immunomodulating agents; other alkylating agents
ATC code:	L01AX03
Route of administration:	Oral
Therapeutic indication:	<i>Adults only</i> - newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment; <i>children from the age of three years, adolescents and adult patients</i> - malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy
Prescription status:	prescription only
Date of authorisation in NL:	12 April 2010
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, ES, HU, IE, IT, LU, PL, PT, RO, SE, and SK
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 member states have granted a marketing authorisation for Temozolomide Ratiopharm 5/20/100/140/180/250 mg capsules, hard, from Ratiopharm Nederland B.V. The date of authorisation was on 12 April 2010 in the Netherlands. The product is indicated for treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

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

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

This decentralised procedure concerns a generic application claiming essential similarity with Temodal, 5, 20, 100, 140, 180 and 250 mg capsules (EU License EU/1/98/096) which have been registered through a centralised procedure by SP Europe since 1999.

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 one bioequivalence study in which the pharmacokinetic profile of two products are compared with the pharmacokinetic profile of the reference products Temodal 20 mg and 250 mg capsules, registered in Germany. 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.

Scientific advice has been given to the MAH on the question whether exemption from bioequivalence studies could be granted for temozolomide.

No paediatric development programme has been submitted. This is not required for generic medicinal products.

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 temozolomide, an established active substance which is not described in the Ph.Eur.* or any other pharmacopoeia. Temozolomide is a white to light tan/light pink non-hygroscopic powder that is slightly soluble in water. The active substance is achiral, but shows polymorphism and nine polymorphic forms have been identified. One polymorphic form is consistently used in the manufacture of the product.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture

The synthesis consists of two steps. A detailed description of the manufacturing process was provided. The MAH has committed to evaluate the limits for total impurities when more data is available.

Quality control of drug substance

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated. The batch analysis data presented in the ASMF comply with the specification provided by the ASMF holder. The control of the drug substance performed by the manufacturer has been satisfactorily described. Batch analytical data from three batches of drug substance analysed by the manufacturer of the drug product have been provided.

Stability of drug substance

Stability data on the active substance have been provided for batches stored for up to 24 months in long term stability condition, and up to 6 months in accelerated stability condition. Based on the stability data presented the proposed a retest period of 3 years is considered acceptable.

* *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

The products are formulated as hard capsules and are packaged in amber glass bottles with white polypropylene child-resistant screw cap equipped with an induction seal of polyethylene. Each hard capsule contains 5, 20, 100, 140, 180, or 250 mg temozolomide.

Temozolomide Ratiopharm 5 mg are hard capsules which have a white opaque body and cap with two stripes in green ink on the cap and with "T 5 mg" in green ink on the body.

Temozolomide Ratiopharm 20 mg are hard capsules which have a white opaque body and cap with two stripes in orange ink on the cap and with "T 20 mg" in orange ink on the body.

Temozolomide Ratiopharm 100 mg are hard capsules which have a white opaque body and cap with two stripes in pink ink on the cap and with “T 100 mg” in pink ink on the body.

Temozolomide Ratiopharm 140 mg are hard capsules which have a white opaque body and cap with two stripes in blue ink on the cap and with “T 140 mg” in blue ink on the body.

Temozolomide Ratiopharm 180 mg are hard capsules which have a white opaque body and cap with two stripes in red ink on the cap and with “T 180 mg” in red ink on the body.

Temozolomide Ratiopharm 250 mg are hard capsules which have a white opaque body and cap with two stripes in black ink on the cap and with “T 250 mg” in black ink on the body.

The excipients are:

Capsule contents - anhydrous lactose, sodium starch glycolate type A, colloidal anhydrous silica, tartaric acid, and stearic acid.

Capsule shell - gelatin, titanium dioxide (E171).

Printing ink:

All strengths – shellac, propylene glycol.

5 mg only - titanium dioxide (E171), yellow iron oxide (E172), indigo carmine aluminium lake (E132).

20 mg only - titanium dioxide (E171), sunset yellow FCF, aluminium lake (E110).

100 mg only - red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171).

140 mg only - indigo carmine (E132) aluminium lake (E110).

180 mg only - red iron oxide (E172).

240 mg only - black iron oxide (E172).

The excipients and packaging are usual for this type of dosage form.

The ratio between amounts of active substance and excipients is the same in the strength in the range 100 mg to 250 mg. The 20 mg strength is not dose proportional to the higher strengths. The 5 mg strength is not dose proportional but amount of active substance is low (5%) and the ratio between excipients is similar to that of the 20 mg strength.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The innovator product, Temodal hard capsules, was authorized through the centralized procedure and therefore the qualitative and quantitative composition of the active substance (temozolomide) and excipients is identical in all member states.

Dissolution studies of the innovator product were carried out. Samples tested were Temodal hard capsules of the strengths 5, 20, 100, 140, 180 and 250 mg. More than 85% of the drug was released in 15 minutes in all three media.

Container closure system

The primary packaging material was chosen with respect to the requirements for packaging of hard capsules. The choice is supported by the results of the stability studies on the finished product packed in glass bottles. Confirmation is provided that the glass bottle meets Ph.Eur. requirements and that plastic components comply with Ph.Eur. requirements for 3.1.3, *Polyolefins* and with Directive 2002/72 as amended (relating to plastic materials intended to come into contact with foodstuffs). Specifications and technical drawings are provided. The control of the container closure system is described adequately.

Manufacturing process

A straight forward manufacturing process was selected for the manufacture of Temozolomide capsules, including defined mixing sequences and filling into pre-printed capsules. The manufacturing process is regarded as a non-complex method. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

Excipients

All of the excipients of the capsule fill and the gelatine of the hard capsules comply with the monographs of the current Ph.Eur. The empty hard gelatine capsules are tested according to an in-house specification

for appearance, identification of gelatine and titanium dioxide, average weight, loss on drying, solubility/disintegration, sulphated ash and microbial quality. The specifications from the supplier are also provided. For the constituents of the printing inks reference is made to relevant US and EEC compendial references. Additionally the colorants used are confirmed to meet purity requirements in directive 95/45/EC.

Quality control of drug product

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. The specifications for description, identification, uniformity of dosage units, water, related substances and microbial limits are deemed justified in line with Ph.Eur. requirements, the applicable guidelines and batch analysis data.

Batch analysis results for two production-scale batches (of each strength) are in accordance with the proposed specifications. Method descriptions and reports on analytical validations are provided. The MAH has committed to evaluate the limits for total impurities when more data is available.

Stability tests on the finished product

Stability data on the product have been provided for batches stored for 12 months under long term stability conditions, and for 6 months under accelerated stability conditions. Based on the stability data presented up to date the shelf-life of 2 years with the storage condition "*Store in the original package. Keep the bottles tightly closed in order to protect from moisture.*" proposed by the MAH is considered acceptable.

The MAH has committed to perform a hold time stability study for the finished product over 12 weeks for one batch of Temozolomide 5 mg capsules and one batch of Temozolomide 250 mg capsules. In addition, the MAH has committed to perform an in-use stability for a period of 3 weeks and submit the results as soon as possible.

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

All raw materials used in the product are of vegetable origin/have demonstrated compliance with commission Directive 2003/63/EC and the *NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products* (EMEA/410/01).

II.2 Non clinical aspects

This product is a generic formulation of Temodal, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 temozolomide 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

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

Bioequivalence study

Temozolomide is a cytostatic agent, and for this reason no routine healthy volunteer bioequivalence study can be conducted. The study-setup is quite different from that routinely encountered in bioequivalence studies. This is mainly caused by the fact that this is a bioequivalence study in glioma and metastatic melanoma who are actually treated with temozolomide. Bioequivalence assessment was integrated into a routine treatment schedule for this disease, consisting of 4-6 5-day treatment cycles, of which one cycle was used to assess bioequivalence. Two strengths were compared in one study, i.e., the 20 and 250 mg

strength. In order to reach the final treatment requirements, multiple 20 mg capsules were administered. This is considered acceptable.

Test products: Temozolomide Ratiopharm 20 mg and 250 mg hard capsules (Ratiopharm Nederland B.V.).

Reference products: Temodal 20 mg and 250 mg capsules (Schering-Plough Ltd., Germany).

The choice of the reference product

Temodal tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

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

Design

A single centre, cross-over, controlled, comparative bioequivalence study was carried out under fasted conditions in 29 (18 male, 11 female) cancer patients, aged 21- 69 years. Temozolomide 250 mg (test 1) and 20 mg (test 2), were tested vs. equal doses of reference formulations. The drugs were administered with 240 ml of water, after an overnight fast of 10 hours. The patients kept a standing position during treatment intake.

Routine treatment schedule

Planned chemotherapy consisted of 4 up to 6 treatment cycles of temozolomide. One treatment cycle comprised of: 200 mg/m² temozolomide orally per day for 5 consecutive days/cycles (aiming at obtaining a final dose of 1000 mg/m² in 5 days), followed by a 23 days treatment interruption (in total one cycle lasts 28 days). Temozolomide was administered in a dose of 200 mg/m² for 5 consecutive days at a 4 weeks interval as multiple of 250 mg or 20 mg hard capsules in cycles 1,3,4 to 6. No blood sampling for PK profiling was performed during these treatment cycles.

Cycle used for bioequivalence

Only in cycle 2 blood sampling for PK evaluation was performed. During treatment cycle 2 the subjects received 1 capsule of either test 1 or reference 1 (250 mg) in a randomised fashion at days 1 and 2 of the cycle, and varying doses of test 2 or reference 2 (20 mg) in a randomised fashion at days 3 and 4 of the cycle. Actual doses provided using the 20 mg capsules ranged from 340-660 mg (17-33 x 20 mg capsules), each patient received the same dose on days 3 and 4. Blood sampling collection for pharmacokinetic evaluation was done during these days. At day 5 of cycle 2 the patients received a combination of test 1 (250 mg) and test 2 (20 mg) products in order to obtain a total dose of 1000 mg/m² in 5 days.

For this bioequivalence assessment only Cycle 2 is considered. Safety parameters collected during cycle 1 and 2 are presented.

In this study there is a washout period of less than one day, since equal doses were administered at subsequent days. However, considering the very short t_{1/2} of temozolomide (approximately 2-3 hours in this study) this is considered acceptable. This is supported by the fact that no carry-over is detected in any patient.

During the pharmacokinetic determination days (days 1 to 4 of the second treatment cycle) venous blood samples were taken at the following time points: before temozolomide administrations (time 0) and at 10 minutes, 20 minutes, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post dose.

The analytical method is adequately validated and 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

Two subjects were drop-outs: the first subject was a drop out since November 2008 due to death (not related to medication), the second drop out was a drop out since December 2008 due to haematological toxicity resulting in not complying inclusion criteria for the next cycle. Twenty-seven patients were eligible for pharmacokinetic analysis.

No data were reported for the temozolomide metabolites AIC (5-aminoimidazole-4-carboxamide) and MTIC (5-(3-methyltriazeno)-imidazole-4-carboxamide). However, conclusions on bioequivalence are only based on parent temozolomide AUC and C_{max}, and therefore this “omission” is without consequences. PK and statistical parameters for temozolomide are summarised in the tables below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of temozolomide for the 20 mg strength under fasted conditions. (actual dose given ranged from 340-660 mg (17-33 x 20 mg capsule)).

Treatment N = 27	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test 2 (20 mg)	41.0 ± 6.3	41.7 ± 6.3	14.1 ± 3.0	0.5 (0.17-1.33)	1.9 ± 0.17
Reference	40.1 ± 5.0	40.6 ± 5.1	13.8 ± 3.5	0.75 (0.33-3.0)	1.9 ± 0.15
*Ratio (90% CI)	1.02 (1.00 - 1.04)	1.02 (1.00 - 1.04)	1.03.2 (0.94 - 1.13)	---	---
CV (%)	4.7	4.7	19.1	---	---
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					

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of temozolomide for the 250 mg strength under fasted conditions.

Treatment N = 27	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test 1 (250 mg)	22.8 ± 5.9	23.5 ± 5.7	7.1 ± 2.7	1.0 (0.33-6.0)	2.1 ± 0.5
Reference	22.7 ± 5.3	23.3 ± 5.3	7.3 ± 2.1	0.75 (0.17-6.0)	2.1 ± 0.3
*Ratio (90% CI)	1.00 (0.96 - 1.04)	1.00 (0.97 - 1.04)	0.94 (0.85 - 1.04)	---	---
CV (%)	8.7	6.9	21.0	---	---
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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25 for both the 20 mg and the 250 mg strength. Based on the pharmacokinetic parameters of temozolomide under fasted conditions, it can be concluded that Temozolomide Ratiopharm 20 mg and 250 mg hard capsules and Temodal 20 mg and 250 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results

A bio waiver was requested for the 5 mg, 100 mg, 140 mg and 180 mg strength. The 100 mg, 140 mg and 180 mg strengths are dose-proportional to the 250 mg. Since the other requirements as stated in the *NfG on the investigation of bioavailability and bioequivalence* are also fulfilled, data obtained for the 250 mg strength can be extrapolated to these strengths.

The 5 mg is not dose proportional and formally, data obtained for the 20 mg strength cannot be extrapolated to the 5 mg strength, since only for the 5 mg strength, and not the 20 mg, the active compound represents less than 5% of the total weight. However, the excipients of the 5 and 20 mg strengths are qualitatively similar. Considering the fact that temozolomide is a BCS (Biopharmaceuticals Classification System) class I drug, absorption is not expected to be affected by the quantitative difference in excipients, and therefore a waiver can be granted for the 5 mg strength as well.

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

Temozolomide was first approved in 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of temozolomide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

SPC

The SPC has been adapted to the latest version of the Temodal SPC. These modifications are deemed acceptable. All sections have been revised as requested. The SPC is considered acceptable.

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 3 participants, followed by two rounds with 10 participants each. Amendments were made between the pilot study and the first test round. Minor changes in the mock-up layout of the PIL were made; subheadings were added or changed in section 2 and 3. Also, 2 questions in the User test questionnaire were rephrased and one question was omitted.

The subjects were recruited by medical specialists who entered names of potential participants into the orangeglobal recruiting platform and database. Participants were finally selected to obtain a group that represented the general population. Inclusion and exclusion criteria are defined and acceptable. The test was performed as face-to-face interviews. There were clear instructions for the interviewer to follow. Subjects were asked to give their answer in their own words and show where in the leaflet the information was found.

The subjects were asked 14 questions related to safety and compliance issues, such as indication, dosage, warnings and side effects plus 3 additional questions regarding the general design and layout of

the leaflet. The questions were open and randomly ordered. The most important aspects of the leaflet are covered by the test, and the questionnaire is considered acceptable.

Both the first and the second test round met the success criteria of 90 % of the subjects being able to locate the requested information, and of those, 90 % being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (content, language and layout) was mostly positive. In conclusion, the user test is considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Temozolomide Ratiopharm 5/20/100/140/180/250 mg capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Temodal, 5, 20, 100, 140, 180 and 250 mg capsules. Temodal 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 SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Temozolomide Ratiopharm 5/20/100/140/180/250 mg capsules, hard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 February 2010. Temozolomide Ratiopharm 5/20/100/140/180/250 mg capsules, hard are authorised in the Netherlands on 12 April 2010.

The first PSUR will cover the period from February 2010 to February 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 23 February 2015.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH has committed to evaluate the limits for total impurities when more data is available.

Quality - medicinal product

- The MAH has committed to perform a hold time stability study for the finished product over 12 weeks for one batch of Temozolomide 5 mg capsules and one batch of Temozolomide 250 mg capsules.

- The MAH has committed to perform an in-use stability for a period of 3 weeks and submit the results as soon as possible.

List of abbreviations

AIC	5-aminoimidazole-4-carboxamide
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BCS	Biopharmaceuticals Classification System
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
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
MTC	Monomethyl Triazenoimidazole Carboxamide
MTIC	5-(3-methyltriazeno)-imidazole-4-carboxamide
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 _½	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
<p>1) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Site where any manufacturing operations take place, except batch-release, batch control, primary and secondary packaging for non-sterile medicinal products.</p> <p>2) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing. Change in the manufacturing process of the finished product - minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.</p>	NL/H/1665/001-006/IB/001/G	IB/G	26-5-2010	25-6-2010	Approval	N