CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Capecitabine Sandoz 150 mg and 500 mg, film-coated tablets Sandoz B.V., the Netherlands

capecitabine

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/2458/001-002/DC
Registration number in the Netherlands: RVG 110880-110881

25 June 2013

Pharmacotherapeutic group:	antineoplastic agents
ATC code:	L01BC06
Route of administration:	oral
Therapeutic indication:	adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer; treatment of metastatic colorectal cancer; first-line treatment of advanced gastric cancer in combination with a platinum-based regimen; in combination with docetaxel for the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy; monotherapy for locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen.
Prescription status:	prescription only
Date of authorisation in NL:	15 May 2013
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LV, MT, PL, PT, RO, SE, SI, SK, UK
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 Capecitabine Sandoz 150 mg and 500 mg, film-coated tablets from Sandoz. The date of authorisation was on 15 May 2013 in the Netherlands.

The product is indicated:

- for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.
- for the treatment of metastatic colorectal cancer.
- as first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.
- in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.
- as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

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

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine has been designed and developed as a pro-drug to the known cytotoxic agent 5-FU and becomes cytotoxic only after conversion to 5-FU. Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product XELODA® 150 mg and 500 mg film-coated tablets which have been authorised in the EEA by Roche Registration Limited since 2 February 2001 (original product). The product was registered through a centralised procedure EU/1/00/163/001-002.

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 XELODA 500 mg tablets registered in the EEA. 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 with respect to these products in 2009 by the German and Dutch regulatory authorities.

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 capecitabine, an established active substance described in the US Pharmacopoeia (USP*). It is a white to off-white powder, which is freely soluble in methanol, soluble in alcohol and acetonitrile and sparingly soluble in water. No polymorphic forms are described in literature. The molecule contains four chiral centers.

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.

Manufacturing process
The capecitabine manufacturing process consists of two stages and has been adequately described. The starting materials, reagents and solvents and intermediates are controlled adequately.

Quality control of drug substance
The drug substance specification is established, but is based on the USP monograph of capecitabine with additional tests on residual solvents. The specifications are acceptable in line with the USP, Ph.Eur., the route of synthesis and the various European guidelines. The analytical methods are adequately described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for eight production-scale batches. The batches were stored at 25°C/60%RH (4 for 36 months, 3 for 9 months and 1 for 3 months) and at 40°C/75%RH (6 months). The accelerated stability data show an increase in impurities, but results remain within limits. From the long-term data, a slight increase in the same impurities was observed. Based on the results, a retest period of 48 months was granted.

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

Medicinal Product

Composition
Capecitabine Sandoz 150 mg is a light pink, film-coated tablet of modified oval shape with the marking "150" on one side.
Capecitabine Sandoz 500 mg is a pink, film-coated tablet of modified oval shape with the marking "500" on one side.

The film-coated tablets are packed in PVC/PVDC-Al foil blisters.

The excipients are:

Tablet core – lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, magnesium stearate
Coating - hypromellose, talc, titanium dioxide (E 171), iron oxide red (E 172).

The tablet cores of the two strengths are dose proportional. The composition of the film-coating differs slightly in the amount of the colouring agents titanium dioxide and iron oxide (red) in order to allow a differentiating of the film-coated tablets.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation and manufacturing process development have been described adequately. Comparative dissolution testing was performed with pilot scale batches against the innovator product. At three different pH values, the profiles can be considered similar. Dissolution profiles wherein the 500 mg bioequivalence test batch is compared with the test batch of the 150 mg strength in order to claim a waiver for the 150 mg strength have been provided; these demonstrating similarity. The waiver is acceptable from a chemical-pharmaceutical point of view. The choice of manufacturing process is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by wet granulation and is initiated by dry mixing of capecitabine with excipients, followed by the addition of binder solution (hypromellose in purified water). After drying and sieving of the granules, more excipients are added and the blend is compressed into tablets, coated and packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for six production-scale batches (three per strength). The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. Opadry coating is not described in common pharmacopoeial monographs, but the individual components have pharmacopoeial monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, dimensions, uniformity of dosage units by mass variation, dissolution, identification (capecitabine and colouring agents), assay, related substances, dissolution and microbiological quality. The release and shelf-life specifications are identical, except for the limits for related substances. The analytical methods have been adequately described and validated. Forced degradation studies have been provided. Batch analytical data from the proposed production site have been provided on the three pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for the three production-scale batches per strength stored at 25°C/60% RH (up to 18 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 PVC/PVDC-Alu blisters.
At accelerated conditions a decrease in assay and an increase in impurities was observed. At long-term conditions no decrease in assay was observed and only a slight increase in the impurities was seen. The results of a photostability study demonstrate that the product is not sensitive to light. Based on the submitted stability data the shelf life of 24 months can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is made from milk sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet. This also applies to the lactose monohydrate included in the Opadry colorants. The used stearic acid for manufacturing of magnesium stearate is of vegetable origin.

Several commitment have been made with regard to the drug product. These are listed on page 9 of this report.

II.2 Non-clinical aspects

This product is a generic formulation of Xeloda, which is available on the European market. No new preclinical data have been submitted. 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 member states 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 capecitabine 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

Capecitabine 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Capecitabine Sandoz 500 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Xeloda 500 mg film-coated tablets (Roche Registration Limited, United Kingdom), from the German market.

The choice of the reference product
The choice of the reference product in the bioequivalence study is accepted, as the product has been registered through a centralised procedure.
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 fed conditions in 104 patients (55 males/49 females), aged 35-80 years, suffering from colorectal cancer or breast cancer.
The recommended dose of capecitabine is 1250 mg/m2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3 week cycles. The dose of capecitabine can be reduced in case of toxicity. In the current study, capecitabine test and reference 500 mg tablets were administered as a single dose of 1500 mg (3 x 500 mg tablet) at an interval of 24 hours as per randomization schedule. The elimination half-life of both parent capecitabine and its metabolite 5-FU is about 0,75 hour.

Test or reference tablets (3 x 500 mg) were administered with 240 ml tap water, 30 minutes after start of the high-calorie, high-fat breakfast.

Subjects received a high-fat, high-calorie (total approximately 800 to 1000 calories) meal in the morning of two subsequent study days denoted –1 and 1 (study period 1 and 2), with approximately 150 calories from protein, 250 calories from carbohydrate, and 500 - 600 calories from fat as recommended by the “Guidance on Bioequivalence”.

For all subjects the type of meal was the same in all periods, and the precise composition of the test meal was identical in all periods for most subjects. Subjects were requested to ingest this meal completely within 30 min or less.

On each PK day, no fluid was allowed from 0 h until 1 h post administration (except for the water given for administration of the drug), from 1h until 6 hour 150 mg water was given every hour. After this time interval water intake was *ad libitum*.

A total of 17 blood samples were collected for each patient in each period. The venous blood samples were withdrawn pre-dose and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, and 8 hours following dose administration.

Capecitabine is a cytostatic agent, and for this reason no routine healthy volunteer bioequivalence study can be conducted. Therefore, the use of patients is accepted. Capecitabine was given at a dose of 1500 mg. A 24 hours washout period was applied between the two administration periods. Considering the capecitabine t1/2 of 0.49 to 0.89 hours (and a t1/2 of 0.7 to 1.3 hours for capecitabine metabolites), this washout period is acceptable. No predose concentrations were observed.
In the provided study, capecitabine was administered with different types of a high-fat meal. All types are of high fat meals applied are considered high-fat, and suitable for its purpose. All patients received the same type of meal in both periods. In conclusion, the study design is acceptable.

Analytical/statistical methods
The analytical methods have been adequately validated and are 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
One hundred patients were evaluable regarding pharmacokinetic profiling. One subject was withdrawn at the end of period 1 due to a serious adverse event (SAE) (pain right hip to the right leg). Three patients were excluded from analysis due to nausea and/or vomiting.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of capecitabine under fed conditions.

Treatment N=100	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4415 ± 1828	4436 ± 1829	3910 ± 2999	1.25 (0.25-4.0)	0.59 ± 0.21
Reference	4311 ± 1795	4368 ± 1795	3608 ± 2376	1.25 (0.25-6.0)	0.58 ± 0.24
***Ratio (90% CI)**	1.02 (0.99-1.06)	1.02 (0.98-1.05)	1.08 (0.98-1.20)	-	-
CV (%)	13.7	13.4	44.5	-	-

$AUC_{0-\infty}$ 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

**ln-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. Based on the pharmacokinetic parameters of capecitabine under fed conditions, it can be concluded that Capecitabine

Sandoz 500 mg and Xeloda 500 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Food effect
In the submitted study, capecitabine was administered with a high-fat, high-calorie meal. This is in accordance with the Guideline on the Investigation of Bioequivalence. According the SPC capecitabine tablets should be swallowed with water within 30 minutes after a meal. Therefore a bioequivalence study under fed conditions is acceptable.

Safety
There were a total of 68 adverse events (AEs) reported in the study, 38 AEs in 21 subjects after test treatment, and 30 AEs in 22 subjects after reference treatment. 21 out of these 68 AEs were suspected to be drug related. 12 out of the 21 drug related AEs were reported after test and 9 after reference treatment. During the study one SAE occurred as "pain right hip to the right leg", which, as it did not respond adequately to treatment, led to hospitalisation. This SAE was not suspected to be related to the drug.
Data from the study demonstrated that both the test and the reference drugs were equally tolerated.

Biowaiver
A biowaiver has been granted for the 150 mg strength, based on the results of the bioequivalence study conducted with the 500 mg strength, with the following justification:

- Capecitabine Sandoz 150 mg & 500 mg tablets are manufactured by the same manufacturer and using the same manufacturing process.
- The qualitative composition of Capecitabine Sandoz 150 mg tablets is the same as that of Capecitabine Sandoz 500 mg tablets.
- Capecitabine Sandoz 150 mg tablets are dose proportional with Capecitabine Sandoz 500 mg tablets. Thus, the ratio between amount of each excipient to the amount of active substance is the same for both the strengths.
- The dissolution profiles of Capecitabine Sandoz 150 mg tablets are similar to Capecitabine Sandoz 500 mg tablets.

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
Capecitabine was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of capecitabine 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

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Xeloda.

Readability test
The package leaflet has not been evaluated via a user consultation study. The proposed PL is textually identical to the leaflet of the originator, *i.e.* Roche's Xeloda (EMEA Product number EMEA/H/C/000316), which was approved during a central procedure. The MAH's package insert house style design and layout used for package insert was successfully tested in more than 50 other approved package insert readability

tests. The positively finalized user tests from these referenced procedures were achieved in recent years. Therefore, the readability of the package insert with the proposed house style is given and no additional user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Capecitabine Sandoz 150 mg and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of XELODA® 150 mg and 500 mg film-coated tablets. XELODA is a well-known medicinal product with an established favorable 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 Capecitabine Sandoz 150 mg and 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 11 March 2013. Capecitabine Sandoz 150 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 15 May 2013.

The date for the first renewal will be: 11 March 2018.

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

Quality - medicinal product

- The MAH committed to provide comparative dissolution profiles in release medium on three consecutive commercial batches by means of an appropriate variation submitted at the latest six months after launch.
- The MAH committed to perform a further process validation on three consecutive batches with focus on compression process before launch and to provide the process validation report to health authorities by means of an appropriate variation submitted at the latest six months after launch in order to demonstrate that the new acceptance values for disintegration time can be met and leads to a product, which complies well with the established finished drug product specifications.
- The MAH committed to perform a bulk stability study investigating the dossier batches of the drug product manufacturer.
- The MAH committed to continue the stability study according to the stability protocol presented.
- The MAH committed that the first three production scale batches with a batch size greater will be subjected to a stability study. The study will be performed according to the stability protocol presented. Additionally one batch per strength per year will be subjected to a stability study.

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
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
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