CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Capecitabine CF 150 mg and 500 mg, film-coated tablets Centrafarm 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/2287/001-002/DC
Registration number in the Netherlands: RVG 109386, 109393

15 August 2012

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:	21 March 2012
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, ES, FR, IT, LU, PT, SE, 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 Capecitabine CF 150 mg and 500 mg, film-coated tablets from Centrafarm B.V. The date of authorisation was on 21 March 2012 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 by 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.

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 capecitabine, an established active substance described in the US Pharmacopoeia (USP*). The active substance 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, and also XRD and DSC difractograms of the material show absence of polymorphism. The molecule contains four chiral centers.

The Active Substance Master File (ASMF) procedure is used for both suppliers of 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 synthesis has been adequately described. The starting materials are deemed acceptable. The active substance has been adequately characterized. The starting materials, reagents and solvents and intermediates are controlled adequately.

Quality control of drug substance
The drug substance specification is established in-house by the ASMF-holders, and is based on the USP monograph of capecitabine with additional tests on residual solvents and microbiological quality. The specification is acceptable, in line with the USP, Ph.Eur., the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches by each ASMF-holder and for a total of 18 batches by the MAH. The analytical methods are adequately described and validated.

Stability of drug substance
For both ASMF-holders, stability data on the active substance have been provided for three production-scale batches. The batches were stored at 25°C/60%RH (36 months or 12 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, no clear trends could be observed. For the first supplier a retest period of 24 months is justified. For the other active substance manufacturer a retest period of 36 months is justified. For both manufacturers, the storage condition is 'Preserved in tight containers, store at controlled room temperature'.

** 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 CF 150 mg is a light peach coloured, oblong shaped, biconvex, film-coated tablet, debossed with "150" on one side and plain on other side.

Capecitabine CF 500 mg is a peach coloured, oblong shaped, biconvex, film-coated tablet, debossed with "500" on one side and plain on other side.

The film-coated tablets are packed in clear PVC/PVdC-Aluminium or Aluminium-Aluminium blisters.

The excipients are:
Tablet core - anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, magnesium stearate
Coating - hypromellose, talc, titanium dioxide (E 171), ferric oxide red (E 172), ferric oxide yellow (E 172).

The two different strengths are dose proportional.

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. In purified water, pH 2 (0.01N HCl), pH 4.5 acetate buffer and phosphate buffer pH 6.8, the profiles can be considered similar. Medium at pH 1.2 (0.1N HCl) was not used as degradation occurs in this medium. The choice of manufacturing process and packaging material 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, followed by the addition of binder solution. After drying and sieving of the granules, the blend is compressed into tablets, coated and packed.
Holding times of the intermediate products have been stated and supported by stability data. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for twelve pilot-scale batches, six per strength and six per manufacturing site. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. and the iron oxides comply with the USP-NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average weight, identification, disintegration time, resistance to crushing, water content, dissolution after 30 minutes, related substances, uniformity of dosage units, assay and microbiological quality. The release and shelf-life specifications are identical, except for the limits for resistance to crushing, water content and related substances. The limits are adequate.
The analytical methods have been adequately described and validated. Forced degradation studies have been provided, demonstrating the stability indicating nature of the HPLC method. Batch analytical data from the proposed production sites have been provided on the twelve pilot-scale batches as used for process validation, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for the twelve pilot-scale batches as used for process validation stored at 25°C/60%RH (up to 12 months), 30°C/65%RH (only for PVC/PVDC-Alu blisters, up to 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 PVC/PVdC-Alu blisters and Alu-Alu blisters. Bulk stability data has been presented up to 6 months at 25°C/60%RH.
The accelerated stability results demonstrate out of specification (OOS) values for the tablets packed in PVC/PVDC-Alu blisters after 3 months for the 150 mg and after 6 months for the 500 mg tablets for

several parameters, including dissolution, impurities, assay and hardness. For the other packaging materials, increase in impurities and decrease in assay is observed, but the results remain within limits.
The intermediate stability data, performed with the PVC/PVDC-Alu blisters only, demonstrate increase in water content and impurities, and decrease in assay, but results remain within limits.
The 24 months of long-term stability results demonstrate slight increase in water content and impurities, and decrease in assay, but the results remain within limits. No significant differences are observed between the container closure systems. The photostability study demonstrates that the drug product is not sensitive to light.
Based on the stability data provided, the claimed shelf life of 36 months, store below 30°C in the two blisters is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Other than anhydrous lactose, for which TSE-free certificate is presented, no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

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, 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 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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Capecitabine CF 500 mg (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product XELODA 500 mg film-coated tablets (manufactured by Roche Pharma AG, Germany) from the UK 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 88 patients (17 males/71 females), aged 27-81 years with locally advanced or metastatic breast cancer or metastatic colorectal cancer under fed conditions. Equal allocation of treatment sequence was as per the randomization schedule. Patients were on an overnight fast for at least 10 hours prior to serving of breakfast on the day of dosing. Patients were served the EMA recommended "standardized non high-fat meal" (about 650 kcal with about 30% of calories derived from fat), which they consumed completely within 30 minutes prior to dosing in each period. At 30 ± 2 minutes after serving of the breakfast, patients were administered a single oral dose of three tablets of either the 500 mg reference product or the 500 mg test product, while in sitting posture, with 240 ± 2 ml of water. Meals were provided to the patients at appropriate times during housing ensuring the requisite fasting criteria.

Patients had no access to drinking water from one hour before to one hour after dose administration (except the 240 ± 2 ml water administered with the dose) in each period. Prior to and thereafter, water was allowed at all times.
Patients were instructed not to lie down and they remained seated for the first 3 hours after dosing on Day 1 and Day 22. Patients were instructed to avoid any strenuous activity throughout their stay.
Thereafter, the patients were allowed to engage only in normal activities while avoiding severe physical exertion.

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.

The recommended dose of capecitabine is 1250 mg/m^2 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 capecitabine tablets were administered as a single dose of 1500 mg (3 x 500 mg tablet) at an interval of 21 days as per randomization schedule. The elimination half-life of both parent capecitabine and its metabolite 5-FU is about 0.75 hour. The patient took either the reference drug or the test drug only as the first dose of each chemotherapy cycle as per randomization schedule. Period I is the first day of the first chemotherapy cycle of the study and Period II is the first day of the next chemotherapy cycle of the study. There was a 7 days washout period between the end of drug administration in the first cycle and the first treatment in cycle 2. This washout period is acceptable

A total of 16 blood samples, each of 3 ml (5 ml for pre-dose sample) were collected for each patient in each period (except for discontinued patients). The venous blood samples were withdrawn pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 5, 6, 8, 10, 12 hours following dose administration.

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
Seventy-three patients were evaluable regarding pharmacokinetic profiling. The reasons for withdrawal were adequately reported.

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

Treatment N=73	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6005 ± 2297	5956 ± 2147	4179 ± 2418	2.0 (0.5-5.0)	0.53 ± 0.22
Reference	6009 ± 2657	6047 ± 2672	4060 ± 2349	2.0 (0.5-4.0)	0.64 ± 0.44
***Ratio (90% CI)**	1.01 (0.96-1.06)	1.00 (0.95-1.05)	1.02 (0.91-1.15)	--	--
CV (%)	19.3	18.2	45.0	--	--

$AUC_{0-\infty}$ 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 fasted conditions, it can be concluded that Capecitabine CF 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 is administered with a moderate fat meal. According to the Guideline on the Investigation of Bioequivalence, in principle a high-fat meal should, be used, but in case of cancer patients, with the incidence of nausea and vomiting being higher than in other populations, a moderate fat meal is agreed. 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 222 adverse events (AEs) reported in the study. Eighty-three AEs were pre-treatment AEs and 139 AEs were treatment emergent AEs. Out of the treatment emergent AEs, 39 were related to the study drug.
Among the total 222 AEs reported during the study, there were 7 deaths and 7 other serious adverse events. Two deaths and two SAEs were judge as related to the study drug.
Some adverse events were unresolved in the trial. Those patients were followed up and advised appropriate treatment. Data from the study demonstrated that both the test and the reference drugs were equally tolerated. Safety is considered within the expected range for this patient population.

Biowaiver
A biowaiver has been granted for the 150 mg strength, based on the result of the bioequivalence study conducted with the 500 mg strength, with the following justification:
- Capecitabine CF 150 mg & 500 mg tablets are manufactured by the same manufacturer and using the same manufacturing process.
- The qualitative composition of Capecitabine CF 150 mg tablets is the same as that of Capecitabine CF 500 mg tablets.
- Capecitabine CF 150 mg tablets are dose proportional with Capecitabine CF 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 CF 150 mg tablets are similar to Capecitabine CF 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 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, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 81% correct answers. The PIL for capecitabine has similar wording as the aproved PIL of Xeloda. The readability test performed shows that no lay-out aspects are negatively influencing the readability of the capecitabine PIL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Capecitabine CF 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 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 Capecitabine CF 150 mg and 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 February 2012. Capecitabine CF 150 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 21 March 2012.

The date for the first renewal will be: 16 February 2017.

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

List of abbreviations

AE	Adverse Event
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
SAE	Serious Adverse Event
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