16 February 2012
EMA/225644/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Capecitabine Accord

International non-proprietary name: **capecitabine**

Procedure No. **EMEA/H/C/002386**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 25 February 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Capecitabine Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 September 2010.

The application concerns a generic and hybrid medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer (see section 5.1).
>
> Capecitabine is indicated for the treatment of metastatic colorectal cancer (see section 5.1).
>
> Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen (see section 5.1).
>
> Capecitabine in combination with docetaxel (see section 5.1) is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine is also indicated 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.

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC. Article 10(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Xeloda instead of non-clinical and clinical data.

Information on paediatric requirements

Not applicable

<u>Capecitabine Accord 150 mg and 500 mg film coated tablets</u>

The legal basis for this application refers to: Article 10(1) of Directive 2001/83/EC

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets

- Marketing authorisation holder: Roche Registration Limited, UK
- Date of authorisation: 02 February 2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/00/163/001 - 002

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
- Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets
- Marketing authorisation holder: Roche Registration Limited, UK
- Date of authorisation: 02 February 2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/00/163/001 - 002

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:
- Product name, strength, pharmaceutical form: Xeloda 500 mg film coated tablets
- Marketing authorisation holder: Roche Registration Limited, UK
- Date of authorisation: 02 February 2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number(s): EU/1/00/163/002
- Bioavailability study number(s): 438-08

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Xeloda instead of non-clinical and clinical unless justified otherwise

Capecitabine Accord 300 mg film coated tablets

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC)

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets
- Marketing authorisation holder: Roche Registration Limited, UK
- Date of authorisation: 02 February 2001

- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/00/163/001 - 002

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets
- Marketing authorisation holder: Roche Registration Limited, UK
- Date of authorisation: 02 February 2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/00/163/001 - 002

■ Difference(s) compared to this reference medicinal product:

☐ changes in the active substance(s)
☐ change in therapeutic indications
☐ change in pharmaceutical form
☒ change in strength (quantitative change to the active substance(s))
☐ change in route of administration
☐ bioequivalence cannot be demonstrated through bioavailability studies

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xeloda 500mg film coated tablets
- Marketing authorisation holder: Roche Registration Limited, UK
- Date of authorisation: 02 February 2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number(s): EU/1/00/163/002
- Bioavailability study number(s): 438-08

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Tomas Salmonson

- The application was received by the EMA on 25 February 2011.
- The procedure started on 23 March 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2011.
- During the meeting on 18 – 21 July 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 July 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 November 2011.
- During the meeting on 12 – 15 December 2011, the CHMP agreed on the consolidated List of Outstanding Issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 15 December 2011.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 January 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 January 2012.
- The Rapporteur circulated an updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 14 February 2012.
- During the meeting on 13 – 16 February 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Capecitabine Accord on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Capecitabine Accord, 150 mg and 500 mg film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC.

Capecitabine Accord, 300 mg film-coated tablets, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. This additional strength is not approved for the reference medicinal product, Xeloda.

The active substance in Capecitabine Accord is capecitabine, a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion of capecitabine 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.

The efficacy and safety of capecitabine has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference medicinal product Xeloda.

The indication proposed for Capecitabine Accord is the same as the authorised indication for the reference medicinal product and includes treatment of colon, colorectal, gastric and breast cancer.

Given as single agent, the recommended starting dose for capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

In combination treatment in colon, colorectal and gastric cancer, the recommended starting dose of capecitabine should be reduced to 800 – 1000 mg/m2 when administered twice daily for 14 days followed by a 7-day rest period or to 625 mg /m2 twice daily when administered continuously. The inclusion of biological agents in a combination regimen has no effect on the starting dose of capecitabine. Premedication to maintain adequate hydration and anti-emesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the capecitabine plus cisplatin combination. Premedication with antiemetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for duration of 6 months.

Finally, in combination with docetaxel, the recommended starting dose of capecitabine in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks. Pre-medication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the capecitabine plus docetaxel combination.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. For further posology recommendations please refer to section 4.2 of the SmPC.

In addition to the 60 and 120 tablet pack presentations authorised for Xeloda, the applicant has applied for a 30 tablet pack size for all strengths (150 mg, 300 mg and 500 mg). The proposed pack sizes are consistent with the dosage regimen and duration of use of the reference medicinal product.

A duplicate Marketing Authorisation Application, Capecitabine KrkA, 150 mg, 300 mg and 500 mg film-coated tablets, was simultaneously under initial assessment making reference to the Capecitabine Accord application.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as film-coated tablets containing 150 mg, 300 mg, and 500 mg of capecitabine as active substance. Other ingredients are:

Tablet core: Anhydrous lactose, cellulose microcrystalline (E460), croscarmellose sodium, hypromellose, magnesium stearate.

Tablet coating: Hypromellose, and colorants.

The tablets are packed in Aluminium- Aluminium and PVC/PVdC-Aluminium blisters packs.

2.2.2. Active substance

This medicinal product contains as active substance capecitabine. The chemical names of capecitabine are: Carbamic acid, [1-(5-deoxy-β-D-ribofuranosyl)-5- fluoro-1,2-dihydro-2-oxo-4-pyrimidinyl]-, pentyl ester, 5'-Deoxy-5-fluoro-*N* [(pentyloxy)carbonyl]cytidine, pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2- dihydro-2-oxo-4-pyrimidine carbamate or N(4)-Pentyloxycarbonyl-5'-deoxy-5-fluorocytidine. The molecular formula is $C_{15}H_{22}FN_3O_6$.

Capecitabine appears as a white to off white crystalline powder and is freely soluble in methanol, soluble in acetonitrile and in alcohol, sparingly soluble in water. Capecitabine is not hygroscopic.

Literature searches have not result in any information that points to the existence of polymorphism of the active substance.

Capecitabine exhibits stereoisomerism due to the presence of three chiral centers. Stereo chemical purity is controlled routinely and also in stability studies by specific optical rotation. Stability data indicates that the stereochemistry is not changed during manufacture or storage of the active substance.

Manufacturing procedure employed consistently affords a single crystalline form of capecitabine as confirmed by X-ray crystallographic pattern of 3 batches of capecitabine.

Manufacture

At the time of the CHMP opinion, the active substance is supplied by two active substance manufacturers. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of an active substance master file (ASMF). The manufacturing process consists of three steps. All manufacturing steps are adequately described. Adequate in process controls are in place and appropriate specifications have been adopted

for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterised.

Specification

The active substance is tested as per in-house specifications. The specifications of the active substance controlled by the manufacture of the finished include tests as: description, solubility, identification (IR, HPLC), water content (Ph Eur), specific optical rotation (Ph Eur), sulphated ash (Ph Eur), heavy metals (Ph Eur), related substances (HPLC), assay (HPLC), residual solvents (GC),and microbial limit test (Ph Eur).

The specifications and tests proposed are compliant with the relevant ICH guidelines and general requirements of Ph.Eur. The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data have been provided by the active substance suppliers on three commercial scale batches. All batches were in compliance with the predefined active substance specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

Stability studies on the active substance manufactured by both manufacturers have been performed at long term (25±2°C/60±5% RH) and accelerated (40±2°C/75±5% RH) conditions on three production batches, respectively packed in the packing intended for marketing. Up to 12 and 24 months of long term stability data, respectively, and up to 6 months of accelerated stability data has been provided, confirming the stability of the active substance. The specifications tested were description, identity (IR ad HPLC), water content, specific rotation, assay (HPLC), related substances and microbiological purity.

The stability data provided support the proposed retest period at the proposed packaging and storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the product development was to formulate a medicinal product essentially similar, robust, stable and bioequivalent to the reference medicinal product.

During development a number of characteristics of the active substance were evaluated to confirm the suitability of the active substance. The effect of the particle size of capecitabine on the quality of the finished product was investigated and dissolution profiles of different particle sizes were studied. A compatibility study was carry out with the active substance and different commonly used excipients at accelerate thermal stress conditions. The study showed that the active substance is compatible with the excipients used in the finished product.

Wet granulation was chosen as manufacturing process based on formulation development trials. The composition of the tablets was optimised during development. The three strengths are dose-proportional.

The tablets used in the bioequivalence study are identical to those intended for marketing.

Dissolution profiles of the 500 mg test- and reference drug products and the other test strengths 150 mg and 300 mg have been provided using purified water, 0.01N HCl, pH 4.5 acetate buffer and pH 6.8

phosphate buffer. The results show that the dissolution profiles are similar and more than 85% is dissolved within 30 minutes.

The excipients used are anhydrous lactose, cellulose microcrystalline, croscarmellose sodium, hypromellose, magnesium stearate, talc, titanium dioxide, iron oxide red, iron oxide yellow and titanium dioxide. All the excipients are controlled in accordance with Ph Eur monographs except for the colouring agents red and yellow iron oxide which are controlled in accordance with monographs in USN.

The choice of the primary packaging material was based on experience of similar kind of product development and marketing strategy. The tablets are packed in Alu-Alu blister and PVC/PVdC-Alu pack. Based on the available stability results no interaction between the finished product and primary containers is expected.

Adventitious agents

None of the materials, except lactose anhydrous, used in this formulation is of human or animal origin. There is no risk of transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE) associated with the active substance and excipients used in this formulation.

It is confirmed by the manufacturer of the lactose that it does not have potential for TSE and is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev2.

Manufacture of the product

The capecitabine film coated tablets are manufactured by wet granulation and the manufacturing process consists of sieving, mixing, granulation, drying, sizing and lubrication prior to compression to tablets and film coating. The granulation and film coating operations may be done in single lot or in sub batches (or lots) based on the capacity of equipment used. The manufacturing process is described in the documentation and a flow diagram of the process is presented.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in three batches of each strength in each manufacturer and is satisfactory. The in process controls are adequate for this product.

The batch analysis data provided show that this tablet can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product specifications include appropriate tests for description, average weight of tablet, identification (IR, HPLC), , identification of colorants, disintegration time (Ph Eur), resistance to crushing (Ph. Eur.), water (Ph Eur), dissolution, related substances (HPLC), uniformity of dosage (Ph Eur)), assay (95.0% - 105.0%, HPLC), and microbiological enumeration test (Ph. Eur.).

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Three production scale batches of the strengths 150 mg and 500 mg manufactured at one of the manufacturing site and three production scale batches of the strengths 150 mg, 300 mg and 500 mg manufactured at the second manufacturing site have been included in the stability program. The batches have been stored in accordance with ICH requirements at long term conditions (25°C ± 2°C / 60% ± 5% RH), intermediate conditions (30°C ± 2°C / 65% ± 5% RH) and accelerated conditions (40°C ± 2°C / 75% ± 5% RH). The tablets have been stored in the packages intended for marketing. Results from two batches of each strength from one of the manufacturing sites stored for 24 months at long term conditions, 12 months at intermediate conditions and for 6 months at accelerated conditions have been presented. And for the third batch 9 months at long term conditions, 9 months at intermediate conditions and for 6 months at accelerated conditions have been provided

Additionally, results from three batches of the strengths 150 mg, 300 mg and 500 mg, from the second manufacturing site, stored at long term conditions for 9 months and at accelerated conditions for 6 month were provided.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non- clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile is being discussed below.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Capecitabine Accord manufactured by Accord Healthcare Ltd is considered unlikely to result in any significant increase in the combined sales volumes for all capecitabine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

For the composition of the products under consideration, capecitabine Accord 150/300/500 mg tablets, the following excipients were used: lactose (anhydrous), cellulose microcrystalline, croscarmellose sodium, hypromellose (E-5), magnesium stearate and purified water. For the film coating: Hypromellose (6cP, talc, titanium oxide, ferric oxide red, ferric oxide yellow and purified water is used. These excipients are used in the manufacturing of oral pharmaceutical products and are all EP listed.

There are three drug-related impurities namely, compound A (USP) 5'-deoxy-5-fluorocytidine; compound B (USP) 5'-deoxy-5-fluorouridine and compound C (USP) 2'3'-O-carbonyl-5'-deoxy-5-fluoro-N4-(pentyloxycarbonyl) cytidine (USP) .The limits of these impurities are higher than recommended by the Note for Guidance on Impurities in New Drug Product /CPMP/ICH/2738/99) with a qualification threshold of 0.15% for drug products with a maximum daily dose of > 2g which is the case for capecitabine tablets (maximum daily dose for normal body surface area person is 4.3 g).

Impurities A and B are metabolites of capecitabine and hence are considered qualified for that reason. For the compound C, due to the nature of the indication and treatment regimen (given in a limited number of days/cycles and known pharmacological/toxicological profile of the parent drug, the level of 0.5% as set by the shelf-life could be considered qualified. This is in line with guidance in ICH S9, which is the relevant guideline to consider for a product used for the present indication.

2.3.4. Conclusion on the non-clinical aspects

In conclusion, the non-clinical overview presented by the applicant is largely based on published scientific literature which is acceptable since capecitabine is a well known active substance. There are no objections to the approval of Capecitabine Accord from a non-clinical point of view. The SmPC of Capecitabine Accord is similar to that of the originator product Xeloda and it is therefore acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing capecitabine. To support the marketing authorisation application the applicant conducted 1 bioequivalence study with cross-over design under fed conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of capecitabine based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

One bioequivalence study was submitted which employed the 500 mg strength. The applicant claimed that bioequivalence for the other strength(s) of 150 mg and 300 mg could be concluded since all conditions for biowaiver of additional strength according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) were fulfilled.

From a pharmacokinetic point of view, biowaiver for the lower strengths is generally accepted if the pharmacokinetics is either linear or non-linear with a more than dose-proportional increase in exposure. The submitted data indicate that the pharmacokinetics of capecitabine is dose proportional and does not change over time over a dosage range of 500 to 3500 mg/m^2/day. This, in addition to the fact that the lower strengths are not used alone, but in combination to attain the desired dose level, renders the biowaiver for the lower strengths acceptable.

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study with the 500 mg tablet (study 438-08).

2.4.2. Pharmacokinetics

Methods

Study design

Study 438-08 was a multicentre, randomised, open label, single-dose, two-period, two-treatment, two-way crossover, bioequivalence study in 88 male and female cancer patients under fed conditions.

The clinical part of the study was conducted between 01 September 2009 and 25 February 2010 at:

Site ID	Study Center
A	Curie Manvata Cancer centre, Opp. Mahamarg Bus stand, Mumbai Naka, Nashik, Maharashtra-422004
B	Deenanath Mangeshkar Hospital & Research Centre, Erandwane, Pune-411004 Maharashtra
C	Kaushalya Medical Foundation Trust Hospital, Ganeshwadi, Bhind Nitin Company, Panchpakadi, Thane (w)-400601
D	Ruby Hall Clinic 40 , Sassoon Road, Pune-411001
E	Shatabdi Super speciality Hospital, Suyojit City Center, Mumbai Naka, Nashik, Maharashtra-422005
F	Dr.Rai Memorial Medical Centre, No: 562 - Century Plaza, Anna Salai, (Opp DMS) Teynampet, Chennai – 600018

G	Meenakshi Mission Hospital and Research Centre, Lake Area, Melur Road, Madurai – 625107
I	Christian Medical College, IDA Scudder Road, Vellore - 632 001.
J	Global Hospital, Lakadi ka pool, Hyderabad- 500004
K	M S Patel Cancer Centre, Shree Krishna Hospital, Gokal Nagar, Karamsad
M	Mahavir Cancer Sansthan, Phulwari Sharif, Patna
O	Jeevandeep Hospital, 302, 3rd floor, Ayush Doctor House, Station Road, Surat
P	Netaji Subhash Chandra Bose Cancer Research Institute, 16A, Park Lane, Kolkata-16

The analytical part of the study was conducted between 20 November 2009 and 17 March 2010 at:

Lambda Therapeutic Research Ltd., Lambda House, Opp. Gujarat High Court, S.G. Highway, Gota, Ahmedabad - 380 061, Gujarat, India

The study lasted through one treatment cycle of capecitabine (2 weeks of daily treatment followed by 1 week rest period); period-I was the first day of the first chemotherapy cycle of the study and Period-II was the first day of the next chemotherapy cycle of the study. Capecitabine was administered in doses of 2500 mg/m^2 / day in two divided doses. The patients were administered either the reference drug or the test drug only as the first morning dose of each chemotherapy cycle as per randomisation schedule as a single dose of 1500 mg.

Patients were on an overnight fast for at least 10 hours prior to serving of a standardised non high-fat breakfast (about 650 kcal with about 30% derived from fat) prior to dosing in each period. At 30 minutes after serving of the breakfast, patients were administered a single oral dose of 1500 mg (3x500 mg) of either the test or reference product, with 240 ml of water. Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.333, 2.667, 3, 3.333, 3.667, 4, 5, 6, 8, 10 and 12 hours following dose administration.

Test and reference products

Capecitabine, 500 mg tablets, manufactured by Intas Pharmaceuticals Ltd, India (batch No. K5123, expiry date: June 2011, assayed content 101.1%) has been compared to Xeloda, 500 mg tablets, manufactured by Roche Pharma AG, Germany (batch No. B1088, expiry date: October 2010, assayed content 97.8%).

Population studied

A total of 88 adult (17 male and 71 female) metastatic breast cancer or metastatic colorectal cancer patients, aged 27-87 years, were enrolled. Out of these, 76 patients completed the PK-part of the study. As samples of three patients reached beyond stability period for analysis, their samples were not analysed. One additional patient received restricted medication during the study and although his samples were analysed, data obtained from the analysis were not considered for the efficacy analysis. Hence, samples from 72 patients were analysed and included in the pharmacokinetic analysis.

The mean age for the 88 patients randomised was 51 ± 12 years, mean height was 153 ± 9 cm, mean weight was 55 ± 10 kg and the mean body mass index (BMI) was 23.4 ± 4.1 kg / m2. The racial make-up of the study was 100% Asian.

Analytical methods

Plasma concentrations of capecitabine and the active metabolite 5-FU were determined with an LC/MS/MS method.

Pre-study validation

Specificity was shown employing eight independent sources of human plasma. Sensitivity at the limit of quantification, 10.239 ng/ml for capecitabine and 5.021 ng/ml for 5-FU, was shown. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Linearity was demonstrated within the calibration range 10.239-5006.536 ng/ml for capecitabine and 5.021-758.504 ng/ml for 5-FU. Dilution integrity for a factor of 5 and 10 was demonstrated. Stability in plasma was demonstrated for 9 h at room temperature, for 91 hours at 2 to 8°C and over three freeze-thaw cycles. There was no interference of co-administration of aspirin, paracetamol, ranitidine, ibuprofen, diclofenac or cetirizine. There was no inter-conversion between capecitabine and 5-FU during sample processing.

Within-study validation

Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. LLOQ was below 1/20 of average C_{max}.

Pharmacokinetic variables

Pharmacokinetic variables were calculated using conventional non-compartmental method. The pharmacokinetic variables included C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, t½ and extrapolated AUC.

Statistical methods

The statistical analysis was performed on log-transformed AUC_{0-t} and C_{max} using ANOVA. The protocol stated that bioequivalence was to be concluded if the 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80.00-125.00% for capecitabine AUC_{0-t} and C_{max}.

Originally a sample size of 110 patients was planned for based on literature data estimating the intra-patient variability of Capecitabine as ~47%. As per protocol an interim analysis for validation of intra-subject variability was performed after completion of 30 patients. The sample size was recalculated using the observed intra-subject variability of 39% and the number of patients was amended (Amendment I, Dec 08, 2009). Based on the interim analysis, 88 patients were required to get data of 72 patients to establish bioequivalence considering the drop-out rate as 20% and hence it was decided to complete the enrolment of 88 patients.

Results

Table 1. Pharmacokinetic parameters for capecitabine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	6005	2297	6009	2657
$AUC_{(0-\infty)}$	5956	2147	6047	2672
C_{max}	4179	2418	4060	2349
T_{max}*	2.0	0.5-5.0	2.0	0.5-5.0
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours (ng*h/ml)			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity (ng*h/ml)			
C_{max}	maximum plasma concentration (ng/ml)			
T_{max}	time for maximum concentration (* median, range) (h)			

The extrapolated AUC was less than 20% in all subjects.

No pre-dose concentrations were detected. Four subjects receiving test and four reference reached t_{max} at the first sampling point.

Table 2. Statistical analysis for capecitabine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.9	95.68-106.46	19.3%
C_{max}	102.1	90.55-115.12	45.0%
* estimated from the Residual Mean Squares			

Table 3. Pharmacokinetic parameters for 5-FU (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	416.7	207.9	391.3	177.8
C_{max}	240.8	177.6	225.2	161.1
T_{max}*	2.333		2.333	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours (ng*h/ml)			
C_{max}	maximum plasma concentration (ng/ml)			
T_{max}	time for maximum concentration (* median, range) (h)			

The extrapolated AUC was >20% for one patient in reference and one patient in test.

No pre-dose concentrations were detected. One subject reached t_{max} at the first sampling point after receiving the reference product.

Safety data

There were a total of 222 adverse events (AEs) reported in the study. 83 AEs were pretreatment AEs and 139 AEs were treatment emergent AEs. Out of the treatment emergent AEs, 39 were related to the study drug. The most frequently treatment emergent AEs were nausea (8 events), vomiting (8 events), constipation (7 events) and anorexia (7 events).

Among the total 222 AEs reported during the study, there were 7 deaths and 7 other serious adverse events (SAEs). Two deaths and two SAEs were judged as related to the study drug.

Conclusions

Based on the presented bioequivalence study Capecitabine Accord is considered bioequivalent with Xeloda.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

In this application no new efficacy or safety data have been submitted and none are required. The applicant has provided an acceptable review of clinical trial published in literature, describing the efficacy and safety profile of capecitabine. No new dose recommendations compared with the reference product have been made for this generic application.

Study 438-08, the pivotal bioequivalence study, was a multicentre, randomised, open label, single-dose, two-period, two-treatment, crossover, bioequivalence study in 88 male and female cancer patients under fed conditions. No issues regarding GCP have been identified with this study. The clinical part of the study was conducted at regular cancer clinics. The bioanalytical facility has been inspected by the WHO, without any critical findings.

A single-dose bioequivalence study is adequate to demonstrate bioequivalence of an orally administered immediate-release formulation. Moreover, as the SmPC of the reference product recommends administration within 30 minutes after a meal, a study in the fed state is appropriate. If no specific recommendation regarding the composition of the meal is given in the SmPC, the guideline on bioequivalence states that a high-fat meal should be administered in the bioequivalence study. However, as the reason for the dosage recommendations in the Xeloda SmPC is to be in line with how the product was administered during the clinical studies, which were most probably not high fat meals, it is considered acceptable to use a non-high fat meal in the bioequivalence study.

Given the fast absorption and short half-life, it could have been considered to include a sampling point earlier than 0.5 h. The relatively sparse sampling is however not considered to be an advantage in the bioequivalence evaluation.

Reasons for withdrawal of patients from the study were according to the protocol and considered acceptable.

For capecitabine 11 samples were reanalysed due to anomalous concentrations. The samples were reanalysed in duplicates and the mean of the repeated value was reported. Reanalysis due to pharmacokinetic reasons are normally not accepted. In this case, the reported values were however in general rather close to the original values and this is not believed to have influenced the overall results.

Data on long-term stability of capecitabine in plasma, covering the actual storage time of study samples (188 days), were provided and stability for 190 days was demonstrated.

As the interim analysis was performed to investigate intra-subject variability and not as an interim analysis of bioequivalence, there is no need to adjust the confidence intervals to preserve the overall type I error.

For capecitabine AUC_{0-t} and C_{max}, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. For a few subjects t_{max} was the first sampling point. The number was equal after administration of the test and the reference product and is not considered to be relevant in the overall evaluation of bioequivalence.

Capecitabine is an orally administered chemotherapeutic agent. It is mainly self-administered by patients in doses 800-1250 mg/m2 twice daily for two weeks followed by one week rest period i 3 weeks cycles. The duration of the treatment can be several months.

The reference product Xeloda has two strengths 150 mg and 500 mg. These tablets differs in size - 150 mg 11,4×5,3 mm, 500 mg 15,9×8,4 mm and are debossed by 150 and 500 on one side.

The new strength that is introduced in this hybrid application has a size in between the previously known strengths but otherwise a similar appearance as the originator tablets. As the introduction of a new strength comes with the change to a generic product this could potentially mislead patient to refer a difference in size to the generic product and not to the strength. As this is a chemotherapeutic agent both over- and under-dosing could lead to detrimental consequences.

To minimise the risk for medication errors with regards to the new strength the applicant has changed the colour of the 300 mg strength to off-white which is considered an adequate measure to minimise the potential risk of medication errors.

2.4.6. Conclusions on clinical aspects

There are no objections to approval from a clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP did not require the applicant to submit a risk management plan because the application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified. The potential risk for medication errors due to the new strength has been minimised with the change of the tablets colour of the 300 mg strength.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 3-yearly cycle. The next data lock point for the reference medicinal product is 31 October 2014.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-risk balance

This application concerns a combined generic and hybrid version of capecitabine film coated tablets. The reference product Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

Capecitabine is indicated for the treatment of metastatic colorectal cancer.

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen.

Capecitabine in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine Accord is also indicated 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

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a multicentre, randomised, open label, single-dose, two-period, two-treatment, crossover design in cancer patients under fed conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. A study in the fed state was considered appropriate, as the SmPC of the reference product recommends administration within 30 minutes after a meal. Choice of dose, sampling points, overall sampling time and wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Capecitabine Accord met the protocol-defined criteria for bioequivalence when compared with Xeloda. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80 to 125%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Capecitabine Accord in the following indication:

Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

Capecitabine is indicated for the treatment of metastatic colorectal cancer.

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen.

Capecitabine in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine Accord is also indicated 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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable