23 January 2014
EMA/CHMP/14148/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeloda

International non-proprietary name: CAPECITABINE

Procedure No. EMEA/H/C/000316/II/0058

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 6 November 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Xeloda	CAPECITABINE	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	II

Submission under article 46 of paediatric regulation (EC) no 1901/2006 of the NO21125 final study report on capecitabine and concomitant radiation therapy in children with newly diagnosed brainstem gliomas.

The requested variation proposed no amendments to the Product Information.

Rapporteur: Harald Enzmann

1.2. Steps taken for the assessment

Submission date:	6 November 2013
Start of procedure:	24 November 2013
Rapporteur's preliminary assessment report circulated on:	20 December 2013
CHMP opinion:	23 January 2014

2. Scientific discussion

2.1. Introduction

Capecitabine is an orally administered precursor of 5-deoxy-5-fluorouridine (5-DFUR), which is preferentially converted to the active compound 5- fluorouracil (5-FU) in malignant tissues by thymidine phosphorylase (dThdPase). After oral administration, capecitabine is rapidly and extensively absorbed, metabolised in the liver to 5-deoxy-5-fluorocytidine (5-DFCR), and then converted to 5-DFUR by cytidine deaminase, which is located principally in hepatic and tumour tissue. The final step (metabolism of 5-DFUR to 5-FU by dThdPase) exploits the higher concentrations of dThdPase in tumour tissues compared with adjacent healthy tissues, thus potentially reducing the exposure to 5-FU in normal tissue compared with tumour tissue. 5-FU acts by inhibiting thymidylate synthase, a key enzyme in the synthesis of thymidine, which forces rapidly dividing cancerous cells to undergo cell death due to the lack of thymidine, necessary for DNA replication.

Xeloda (capecitabine) is indicated as adjuvant treatment of patients with colon cancer, for the treatment of patients with metastatic colorectal cancer and as first-line treatment of patients with advanced gastric cancer. Capecitabine is also indicated 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. 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.

With this variation application, the MAH submitted the final clinical study report (CSR) of the paediatric phase II study NO21125 under Article 46 of Regulation (EC) No. 1901/2006. This was a study investigating Xeloda in combination with radiation therapy in paediatric patients with brainstem gliomas. In the EU, there is no Paediatric Investigation Plan in place for Xeloda and there is no relevant use of Xeloda in the paediatric population for all approved indications.

2.2. Clinical aspects

2.2.1. Methods – analysis of data submitted

Study NO21125 was a single arm, multicentre, open label trial with two treatment phases: a radiotherapy [RT] phase [9 weeks treatment + 2-week break] and a post-RT phase [9 weeks].

Main inclusion criteria comprised the following: Paediatric patients (≥3 and <18 years of age) with newly diagnosed non-disseminated brains stem cell glioma (IBSG, histopathologic diagnosis was not required); Performance status: Karnofsky Performance Scale (if >16 years) or Lansky Performance Score (if ≤16 years) ≥50%; Patients must not have had received any prior chemotherapy, RT, immunotherapy or bone marrow transplantation for the treatment of their brainstem glioma; Prior dexamethasone and/or surgery were allowed; Patients must have had adequate organ function (haematologic, hepatic and renal) as further defined in the inclusion criteria.

Dosing of capecitabine differed in the two treatment phases (starting dose 1300 mg/m^2 daily in RT phase and 2500 mg/m^2 daily in the post-RT phase), i.e. capecitabine was administered not only concomitantly with RT but at lower doses in combination with RT.

Primary objective of the trial was:

- To estimate the progression-free survival (PFS) distribution for newly diagnosed patients with diffuse intrinsic brainstem gliomas treated with the combination of capecitabine and radiation therapy (RT) and compare to PBTC historical controls.

Secondary objectives of the trial were:

- To estimate the overall survival (OS) distribution and to summarize the best tumour responses observed prior to failure.
- To further characterise the safety profile of capecitabine administered concomitantly with RT in this paediatric patient population.
- To further characterise the pharmacokinetics of capecitabine and its metabolites as delivered by capecitabine paediatric film-coated tablets (referred to as capecitabine Rapidly Disintegrating Tablets [RDT] in the protocol) in this paediatric population.
- To explore the exposure-response relationship for measures of safety and effectiveness using pharmacokinetic and pharmacodynamic (PK/PD) models.

- Describe diffusion tensor imaging findings at diagnosis and explore early post-irradiation changes as a response measure in brainstem gliomas.

2.2.2. Results

A total of 35 patients were enrolled in protocol NO21125 (from 28 January 2010 through 23 May 2011). One patient did not receive study treatment, and thus 34 patients were included in the ITT population. In addition, 10 patients enrolled in protocol NO18517 (the phase I study) diagnosed with non-metastatic IBSG who received 650 mg/m^2/dose BID capecitabine were included for analysis of efficacy and safety.

A total of 15 patients enrolled in study NO21125 provided PK data.

Capecitabine was rapidly absorbed and converted to its metabolites. Capecitabine and metabolite PK parameters could not be derived from all subjects and the limited sampling schedule meant that robust parameters in all patients could not be obtained by NCA analysis alone. The parameters obtained are summarised in the table below.

Table 1: Mean (CV%) capecitabine and metabolites plasma PK parameters following administration of 650 mg/m^2 capecitabine/day

Day	N	C_{max} (ng/mL)	N	t_{max}[a] (h)	N	AUC_{0-6h} (ng/mL)	N	$t_{1/2}$ (h)
				Capecitabine				
1	15	5290 (94.9)	15	0.500 (0.183-1.27)	10	6180 (67.2)	10	1.83 (97.0)
14	14	3030 (63.6)	14	0.658 (0.167-3.52)	10	6340 (71.5)	6	1.11 (28.8)
				5'-DFCR				
1	15	2830 (62.3)	15	0.500 (0.250-1.27)	10	5260 (73.5)	10	1.58 (66.8)
14	14	2450 (57.2)	14	1.00 (0.167-3.52)	11	5120 (53.6)	4	1.12 (33.3)
				5'-DFUR				
1	15	3750 (52.8)	15	0.500 (0.250-1.27)	8	5920 (53.5)	8	1.76 (59.0)
14	14	3370 (79.7)	14	1.00 (0.250-3.52)	8	5450 (44.4)	2	1.25 (47.8)
				5-FU				
1	15	122 (114)	15	0.856 (0.250-3.00)	6	121 (33.8)	5	1.72 (47.4)
14	14	138 (122)	14	0.883 (0.167-3.52)	9	178 (39.6)	4	1.32 (55.5)
				FBAL				
1	15	1580 (33.7)	15	2.43 (0.833-6.00)	11	5600 (35.7)	3	2.30 (42.1)
14	14	1900 (37.4)	14	3.00 (0.750-6.00)	12	6840 (32.2)	3	1.92 (5.69)

[a] Median (min - max)

For the modelling and simulation analysis, despite the large variability observed mainly in the population predictions, a good agreement between the prediction and the observation was observed and it was concluded that the model previously developed in adults can accurately describe the data collected in the Phase I and Phase II paediatric studies. In the analysis of exposure-safety and exposure-efficacy relationships, no clear relationship between AUC and PFS and tumour size or between AUC and selected AEs was observed although the small sample size precluded any firm conclusions from being drawn (data not shown).

The 1-year Kaplan-Meier estimate for PFS in the ITT population was 8% (90% CI: 1-14%). As the 1-year PFS rate was not above 30.9% (the 1-year Kaplan-Meier estimate for PFS defined in the protocol as 15% above the historical control group), and the lower limit of the associated 90% CI was not above 15.9% (the protocol-defined PFS for the historical control group), the primary study endpoint was not met.

The 1-year Kaplan-Meier estimate for OS was 42% (90% CI: 29-55%). The 1-year Kaplan-Meier estimate was less than 45.6%, which was the protocol-defined 1-year Kaplan-Meier estimate for the historical control group.

Tumour response was based on investigator's assessments. One patient in the ITT population partially responded to treatment and 6 patients had stable disease as best response. None of the patients had a complete response.

The primary toxicities observed included vomiting (reported in 35/44 patients [80%]), alanine aminotransferase increase (33/44 patients [75%]), lymphocyte count decrease (32/44 patients [73%]), white blood cell count decrease (27/44 patients [61%]), and platelet count decrease (25/44 patients [57%]). The SAEs reported within 30 days of last dose of capecitabine mainly included neutrophil count decrease (5/44 patients [11%]), central nervous system (CNS) necrosis (3/44 patients [7%]) and hydrocephalus (3/44 patients [7%]). Five patients withdrew due to AEs (neutrophil count decreased [2 patients], CNS necrosis [1 patient], nail infection [1 patient] and somnolence [1 patient]). One patient died of an AE occurring within 30 days of last treatment administration (clostridial infection considered as related to study drug) during the study.

2.2.3. Discussion

The rationale behind the combination of capecitabine with radiotherapy (RT) is that RT would be expected to increase thymidine phosphorylase (dThdPase) but not dihydropyrimidine dehydrogenase (DPD) acitivity. This would lead to increased concentration of 5-FU selectively in the neoplastic tissue, thus leading to additive-to-synergistic tumour regression (at least as shown in animal tumour models) by capecitabine but not 5-FU. Study NO21125 was designed following this rationale.

Comparison of available pharmacokinetic data in adults with the paediatric data from study NO21125 above suggested that the pattern of metabolism seemed to be similar in children and adults while exposure (to capecitabine) on a dose-normalised basis seemed to be slightly higher in the paediatric population.

With regard to efficacy, addition of capecitabine to RT clearly did not improve the 1-year PFS or OS in children with IBSG.

On safety aspects, typical capecitabine toxicities include dose limiting hand-foot syndrome and gastrointestinal AEs such as diarrhoea and they are not on the level of lymphocyte (or white cell in general) counts, vomiting, or neurological AEs, as observed in study NO21125. Since the study did not have a radiotherapy-only control arm it is rather difficult to actually and reasonably attribute observed AEs to (low dose) capecitabine (monotherapy). Instead, safety data deriving from study NO21125 seem to rather describe more AEs of RT, and are, thus, not contributing relevantly to the safety profile of the Xeloda Product Information.

2.3. Changes to the Product Information

The MAH proposed no changes to the Product Information, which was considered acceptable.

3. Overall conclusion and impact on the benefit/risk balance

The efficacy data of study NO21125 showed that, as an antimetabolite, capecitabine did not show any clinical benefit to paediatric patients with brain tumours when administered concomitantly with radiotherapy (RT), despite the fact that RT increases TS activity. In principle, this conclusion applies also to the adult population (although not investigated to date). In terms of safety, the results of study NO21125 do not alter the risk of Xeloda in the labelled indications.

Overall, the CHMP was of the opinion that the results of study NO21125 have no impact on the risk/benefit balance of Xeloda in its approved indications. No change to the Product Information was considered necessary based on these results.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		**Type**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	II

Submission under article 46 of paediatric regulation (EC) no 1901/2006 of the NO21125 final study report on capecitabine and concomitant radiation therapy in children with newly diagnosed brainstem gliomas.

The requested variation proposed no amendments to the Product Information.

5.