19 April 2018
EMA/164384/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Mylotarg (gemtuzumab ozogamicin)
Treatment of acute myeloid leukaemia
EU/3/00/005 (EMEA/OD/022/00)
Sponsor: Pfizer Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Active substance	Gemtuzumab ozogamicin
International Non-Proprietary Name	Gemtuzumab ozogamicin
Orphan indication	Treatment of acute myeloid leukaemia
Pharmaceutical form	Powder for concentrate for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L01XC05
Sponsor's details:	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Wyeth Europa Limited
COMP opinion date	13 September 2000
EC decision date	18 October 2000
EC registration number	EU/3/00/005
Post-designation procedural history	
Transfer of sponsorship	Transfer from Wyeth Europa Limited to Pfizer Limited – EC decision of 15 March 2013
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	N. Nagercoil, S.B. Sarac
Applicant	Pfizer Limited
Application submission date	1 December 2016
Procedure start date	23 December 2016
Procedure number	EMA/H/C/004204
Invented name	Mylotarg
Therapeutic indication	Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL). Further information on Mylotarg can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	22 February 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	E. Penninga, K. Penttila
Sponsor's report submission date	16 November 2017
COMP discussion	13-15 February 2018
COMP opinion date	27 February 2018

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2000 was based on the following grounds:

- acute myeloid leukaemia (hereinafter referred to as" the condition") was estimated to affect not more than 0.66 in 10,000 persons in the Community when the submission was made;
- the condition is life-threatening: disease-free survival at 7 years is about 40-50% in younger patients. The prognosis is worse for older patients;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that gemtuzumab ozogamicin may be of significant benefit to those affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The COMP continues to accept the condition for orphan designation. Acute myeloid leukaemia (AML) is a disease characterised by rapid, uncontrolled proliferation of malignant clonal haematopoietic stem cells that accumulate as immature, undifferentiated cells (blasts) and lead to impaired production of normal haematopoietic elements, which in turn leads to anaemia, neutropenia, and thrombocytopenia.

The approved therapeutic indication "Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, *de novo* CD33 positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL)" falls within the scope of the designated orphan indication "treatment of acute myeloid leukaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The condition has been presented to be life threatening with a 5-year survival rate of patients of 23% in patients below 55 years of age and 11% for patients above 55 years of age. It is also described that improved survival in the elderly has not substantially changed in the recent years.

Table 1. 5-year AML Survival Rates in the European Union by Age (Maynadie et al Haematologica 2013;98(2):230-8.)

Age (years)	5-Year Survival Rate
0-14	65.52% (range: 59.54%, 70.83%)
15-24	50.92% (range: 43.44%, 57.91%)
25-64	26.98% (range: 25.34%, 28.63%)
≥65	3.86% (range: 3.27%, 4.52%)

The COMP concluded the condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

Number of people affected or at risk

A systematic literature search was conducted to identify epidemiological literature sources. National and pan European registry data were presented from the following sources: Swedish AML registry, NORDCAN, Haematological Malignancy Research Network (UK), RARECARE, HAMECARE. The reported prevalence was in a range of 0.9 per 10,000 population to 1.5 per 10,000 population (table 2). The project Surveillance of Rare Cancers in Europe (RARECARE) project reported a prevalence of 1.1 per 10,000. This prevalence figure was considered to be most relevant, because it is based on data collected in 89 population based cancer registries in 21 European countries.

In addition, a sensitivity analysis was presented taking into consideration the most conservative assumptions. This analysis concluded on a maximum prevalence of 2.5 per 10,000 at the time of application submission in 2017. This figure was estimated by combining the highest reported prevalence figure in Europe of 2015 (1.5 per 1,000) with the highest reported incidence figure (0.5 per 10,000) for years 2016 and 2017. This prevalence estimate could represent an overestimate, but was acknowledged as supportive evidence.

The COMP accepted a prevalence calculation of approximately 1 per 10,000, based on the reported 15 year prevalence from RARECARE.

Table 2. Non-interventional Studies Identifying Prevalence of AML in the European Union

Country	Year of Publication	Study Population	Prevalence Year; Prevalence Rate per 10,000 Population
Sweden (Juliusson et al, 2017)	2017	The Swedish AML registry was utilised to identify and characterise Swedish citizens surviving on 01 January 2014 after an AML diagnosis made during 1997-2013 (n = 1337). Median age of diagnosis was 51 years.	2014; 1.4
Nordic countries (Engholm et al, 2016; Engholm et al 2010)	2017[§]	The NORDCAN database and program provides data from the national cancer registries in Denmark, Finland, Iceland, Norway, Sweden, and Faroe Islands. Prevalence data for AML age-standardised to European population for ages 0 to ≥85 years were reported. No overall data for Sweden or Faroe Islands were reported.	2014; Denmark: 1.3 Finland: 1.2 Iceland: 1.2 Norway: 1.0
United Kingdom (Roman et al, 2016)	2016	Data are from the United Kingdom's population-based Haematological Malignancy Research Network for patients diagnosed with myeloid malignancies from 2004-13 and followed through to 2015. A total of 1411 patients with AML were identified with a median diagnostic age of 70.6 years. Incidence: 0.5 per 10,000 population per year.	2015; 0.9 per 10,000 within 10 years of diagnosis.
Italy (Trama et al, 2012)	2012	The project surveillance of rare cancers in Italy (RITA) collaborated with the RARECARE project. Data was pooled from 20 Italian cancer registries for all ages. To estimate prevalence, only cancer registries that provided cases for the period 1988-2002 were used. Prevalence was calculated at the index date of 01 January 2003. Incidence: 0.5 per 10,000 population per year.	2003; 1.5
European Union (Visser et al, 2012, Gatta, 2011)	2012	Surveillance of Rare Cancers in Europe (RARECARE) collected data on cancers from 89 population-based cancer registries in 21 European countries diagnosed from 1978-2002 for all ages. The mean population covered 32% of the EU-27 population. Incidence: 0.4 per 10,000 population per year.	Estimated prevalence for EU-27 in 2008; 1.1

[§]NORDCAN (http://www.ancr.nu) accessed 31 March 2017.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The following products can be identified to be authorised for the treatment of the orphan condition: histamine dihydrochloride, decitabine, azacitidine, daunorubicin, idarubicin, mitoxantrone, etoposide, cytarabine (Ara-C), thioguanine, L-asparaginase, doxorubicin, vincristine sulphate, cyclophosphamide.

Most recently Rydapt (midostaurin) has been authorised in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive.

The COMP also takes into consideration the current European Society for Medical Oncology (ESMO) treatment guideline from Fey and Buske 2013 discussing the current treatment options for AML in adult patients (Ann Oncol 2013; 24 (Suppl 6): vi138-vi143).

Significant benefit

Significant benefit needs to be demonstrated in adult patients with previously untreated, de novo acute myeloid leukaemia. In this context the ESMO guideline outlines that for intensive treatment of non-APL AML induction should include an anthracycline (daunorubicin) and cytarabine (Ara-C) with the particularly well-known and time-honoured '3+7' regimen. Furthermore, consolidation therapy in AML is warranted once patients have reached clinical and haematological remission. Taken into consideration the ESMO guideline and the authorisation status of medicinal products, it was considered that significant benefit would need to be established versus standard induction chemotherapy consisting of anthracyclines and cytarabine, and midosturin. A demonstration of significant benefit over first line therapies in non-intensive treatments and treatments authorised in the relapsed/refractory setting were not deemed necessary.

Significant benefit versus midostaurin (Rydapt) is argued on a clinically relevant advantage in patients, who are not FLT3 mutation positive. Mylotarg aims to treat naïve patients on top of standard induction chemotherapy with cytarabine and daunorubicin. Midostaurin is indicated for the same line of treatment, but the indication of midostaurin is restricted to patients with FLT3 mutations. Mylotarg can be used for the treatment of all patients independent of FLT3 mutation status and the COMP considered that this represents a clinically relevant advantage.

Significant benefit versus the induction therapy anthracycline (daunorubicin) and cytarabine (Ara-C) was supported by the clinical trial ALFA0701 trial. This trial that was assessed as pivotal evidence by the CHMP (please also refer to the EPAR of Mylotarg). The ALFA0701 trial was an open-label, randomised controlled phase 3 study comparing fractioned low dose Mylotarg in addition to induction and consolidation chemotherapy in patients with de novo untreated AML age 50-70 years. The treatment algorithm was according to clinical practise consisting of the well-known and authorised '3+7' induction chemotherapy (DNR 60 mg/m^2/day and AraC 200 mg/m^2/day with or without Mylotarg 3 mg/m^2/day at Days 1, 3 and 7; max 5mg per dose and day). Primary endpoint was event-free survival (EFS), defined as the time from date of randomisation to date of induction failure, relapse, or death due to any cause, whichever came first, determined by each investigator individually and

according to Guideline recommendations. Follow-up therapies, which could potentially impact EFS analysis, were equally balanced between arms.

A total of 271 patients were included as recruited, randomised and assigned treatment (136 to control, 135 to Mylotarg arm) across 26 sites in France, forming the modified intention to treat (mITT) analysis (excluding the 9 patients without informed consent found). The primary efficacy analysis, investigators review and data cut of August 2011 showed an EFS difference of 7.8 months (hazard ratio [HR] 0.562; 95% confidence interval [CI]: 0.415-0.762; 2-sided p = 0.0002), corresponding to a 44% reduction in the risk of an event for patients in the Mylotarg arm (table 3). The robustness of the EFS was confirmed by appropriate additional sensitivity analyses. Subgroup analyses of EFS indicated a more encouraging treatment effect with the Mylotarg combination in patients with favourable/intermediate risk cytogenetics (HR 0.591; 95% CI (0.407, 0.857), p = 0.0047; vs unfavourable HR 1.08).

Table 3. Event Free Survival Primary Endpoint by Investigator Assessment, mITT Population- (ALFA0701 study)

	GO + Daunorubicin + Cytarabine (N=135)	Daunorubicin + Cytarabine (N=136)
Number of events, n (%)	73 (54.1)	102 (75.0)
Induction failure	17 (12.6)	29 (21.3)
Relapse	44 (32.6)	58 (42.6)
Death	12 (8.9)	15 (11.0)
Number of censored patients, n (%)	62 (45.9)	34 (25.0)
Reason for censoring, n (%)		
Event-free at reference date	62 (45.9)	34 (25.0)
Event-free at last assessment prior to reference date	0	0
No on-study disease assessment	0	0
Patient withdrew consent	0	0
Lost to follow-up	0	0
KM estimate of median time to event (months) [95% CI][a]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
Probability of being event-free at 2 years [95% CI][b,c]	42.1 [32.9, 51.0]	18.2 [11.1, 26.7]
Probability of being event-free at 3 years [95% CI][b,c]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Versus daunorubicin + cytarabine – unstratified		
Hazard ratio[d] [95% CI]	0.562 [0.415, 0.762]	
p-Value[e]	0.0002	
Versus daunorubicin + cytarabine – stratified by risk (NCCN guideline)		
Hazard ratio[d] [95% CI]	0.575 [0.418, 0.790]	
p-Value[e]	0.0006	
Versus daunorubicin + cytarabine – stratified by risk (ELN guideline)		
Hazard ratio[d] [95% CI]	0.559 [0.408, 0.767]	
p-Value[e]	0.0003	

Source: Table 14.2.1.1

Based on the primary definition of EFS: event dates (induction failure, relapse, or death) determined by investigator assessment and censoring date being the reference date of 01 Aug 2011 or the last disease assessment date before the reference date where patient was event-free (no induction failure, relapse, or death). If data existed after reference date confirming the patient was event-free, patient was considered event-free at reference date; otherwise, patient was event-free at the last assessment prior to reference date.

Abbreviations: CI=confidence interval; EFS=event-free survival; ELN=European LeukemiaNet; GO=gemtuzumab ozogamicin; KM=Kaplan-Meier; mITT=modified intent-to-treat; n=number of patients; N=number of patients; NCCN=National Comprehensive Cancer Network.

a. Based on the Brookmeyer and Crowley Method with log-log transformation.

b. Estimated from the KM curve.

c. Calculated from the product-limit method/Calculated from the log[-log(x-<year,month> survival probability)] using a normal approximation and back transformation.

d. Based on the Cox Proportional Hazards Model.

e. 2-sided p-value from the log-rank test.

Regarding the secondary endpoints, relapse-free survival (RFS) confirmed a statistical significant difference in favour of the Mylotarg arm (HR 0.656, 95% CI [0.466, 0.922], p = 0.02480). Response rate, including early response (CR/CRp at Day 15 as part of a post hoc analyses) and overall survival (OS) did not show any statistically significant difference. Survival data are available up to April 20130 and can be considered mature.

In addition to the ALFA0701 trial data, an individual patient data (IPD) meta-analysis from 5 randomised investigator-initiated research (IIR) studies, including the pivotal Study ALFA-0701, was provided. The primary endpoint OS was significantly improved in patients randomised to Mylotarg than

in No-Mylotarg patients. The OR for Mylotarg versus No-Mylotarg was 0.91 (95% CI: 0.84-0.99, p = 0.02), in favour of the Mylotarg arm. Overall pooled median OS was 23.62 months (95% CI: 21.22-27.33) in the Mylotarg arm and 21.49 months (95% CI: 19.42-23.20) in the No-Mylotarg arm.

Taking into consideration the clinical data submitted to the COMP and the CHMP assessment of the benefit-risk, the COMP established significant benefit of Mylotarg based on a clinically relevant advantage as add-on therapy to standard induction chemotherapy with cytarabine and daunorubicin.

4. COMP position adopted on 27 February 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of acute myeloid leukaemia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, Mylotarg is of significant benefit to those affected by the orphan condition. The Committee concluded that Mylotarg offers a clinically relevant advantage for the treatment of adult patients with previously untreated, de novo acute myeloid leukaemia. It was demonstrated that the addition of Mylotarg to authorised induction chemotherapy with daunorubicin and cytarabine led to improved event-free survival when compared to standard chemotherapy alone. In addition, Mylotarg has significant benefit over midostaurin (Rydapt), because it can be used in combination with induction therapy in all treatment-naïve patients, independent of their FLT3 mutation status.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Mylotarg, gemtuzumab ozogamicin, EU/3/00/005 for treatment of acute myeloid leukaemia is not removed from the Community Register of Orphan Medicinal Products.