23 August 2018
EMA/496701/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Vyxeos (Liposomal combination of cytarabine and daunorubicin)
Treatment of acute myeloid leukaemia
EU/3/11/942 (EMA/OD/070/11)
Sponsor: Jazz Pharmaceuticals Ireland Ltd

Note

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

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1. Product and administrative information

Product	
Active substance	Liposomal combination of cytarabine and daunorubicin
International Non-Proprietary Name	Daunorubicin / cytarabine
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)	L01XY01
Sponsor's details:	Jazz Pharmaceuticals Ireland Ltd Fifth Floor, Waterloo Exchange Waterloo Road Dublin 4 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Celator (UK) Ltd
COMP opinion date	09 November 2011
EC decision date	11 January 2012
EC registration number	EU/3/11/942
Post-designation procedural history	
Transfer of sponsorship	Transfer from Celator (UK) Ltd to Jazz Pharmaceuticals Ireland Ltd – EC decision of 19 December 2016
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Robert James Hemmings, Tuomo Lapveteläinen
Applicant	Jazz Pharmaceuticals Ireland Ltd
Application submission date	02 November 2017
Procedure start date	23 November 2017
Procedure number	EMEA/H/C/004282
Invented name	Vyxeos
Therapeutic indication	Vyxeos is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) Further information on Vyxeos 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	28 June 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	Daniel O'Connor/Bozenna Dembowska-Baginska
Sponsor's report submission date	02 November 2017
COMP discussion and adoption of list of questions	13-15 March 2018 17-19 April 2018
COMP opinion date	02 July 2018

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

- acute myeloid leukaemia (hereinafter referred to as "the condition") was estimated to be affecting not more than 1.2 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life threatening due to several consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that liposomal combination of cytarabine and daunorubicin may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the combination of cytarabine and daunorubicin at a ratio of 1 to 5 in liposomes over the standard of care. This is based on preliminary clinical data.

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

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 COMP continues to accept AML as orphan condition for designation.

The approved therapeutic indication "Vyxeos is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)" falls within the scope of the designated orphan indication "Treatment of acute myeloid leukaemia".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

The condition was presented by the sponsor to be chronically debilitating due to neutropenia, anaemia, and thrombocytopenia. Patients typically present with signs and symptoms of fatigue, weakness, haemorrhage, and infection resulting from reductions in red blood cells, platelets or white blood cells. AML was also presented to be life threatening with survival being mainly dependent on the stage (initial diagnosis/first-line vs. relapsed or refractory/second-line and later treatment) and karyotype of

the disease. If untreated, patients may die of infections, complications of infections (e.g. sepsis and multisystem organ failure), or bleeding events (typically central nervous system, respiratory, or gastrointestinal bleeding).

The COMP concluded that 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 a few months if left untreated. Despite the availability of satisfactory methods of treatment, 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. Furthermore, epidemiological data from national registry databases and pan-European databases have been identified. Prevalence figures of AML and its subpopulations have been pooled from the major European registries (table 1). For countries, where there is insufficient data available, figures were estimated based on the EU28 5-year prevalence figure, which was extrapolated for 3 and 10-year prevalence based on registry data. Using crude rates from the incidence data a prevalence figure for each country were determined. The 10-year prevalence figures range up to 1 per 10,000. Based on the presented data a prevalence of approximately 1 per 10,000 was considered to be most representative prevalence figure.

Table 1. Data sources for prevalence estimation

Country	**Source**
Denmark	ANRC (2014). 'NORDCAN 2014', www.ancr.nu
Finland	ANRC (2014). 'NORDCAN 2014', www.ancr.nu
Italy	Associazione Italiana dei Registri TUMori (AIRTUM) (2014). 'AIRTUM I numeri del cancro in Italia - 2013', http://itacan.ispo.toscana.it,
Sweden	ANRC (2014). 'NORDCAN 2014', www.ancr.nu
UK	Epidemiology & Cancer Statistics Group (2004-2014). 'HMRN 2004-2014', www.hmrn.org
EU28	Visser O et al. 2012

Table 2. Prevalence figures for EU

Country	Incidence Rate	Prevalence			Source Year
		3-year	5-year	10-year	
Austria	0.23	2.28	2.93	4.74	-
Belgium	0.41	4.08	5.25	8.49	-
Bulgaria	0.16	1.60	2.06	3.34	-
Croatia	0.18	1.83	2.35	3.80	-
Cyprus	0.27	2.71	3.49	5.64	-
Czech Republic	0.16	1.54	1.99	3.22	-
Denmark	0.27	3.30	4.70	7.20	2015
Estonia	0.25	2.44	3.14	5.08	-
Finland	0.27	3.10	4.10	6.40	2015
France	0.38	3.81	4.91	7.94	-
Germany	0.30	2.97	3.82	6.18	-
Greece	0.50	4.94	6.36	10.28	-
Hungary	0.20	1.98	2.55	4.12	-
Ireland	0.14	1.41	1.82	2.94	-
Italy	0.35	3.51	5.20	7.70	2006
Latvia	0.24	2.34	3.01	4.87	-
Lithuania	0.28	2.82	3.63	5.87	-
Luxembourg	0.34	3.39	4.36	7.05	-
Malta	0.26	2.60	3.35	5.41	-
Netherlands	0.34	3.36	4.33	7.00	-
Poland	0.15	1.49	1.92	3.11	-
Portugal	0.30	2.96	3.82	6.17	-
Romania	0.15	1.49	1.92	3.10	-
Slovakia	0.20	1.98	2.55	4.12	-
Slovenia	0.17	1.72	2.22	3.58	-
Spain	0.32	3.18	4.10	6.62	-
Sweden	0.32	3.90	5.30	8.10	2015
United Kingdom	0.41	4.30	5.50	8.60	2014
EU28	0.37	3.65	4.70	7.6	2008

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 were 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.

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.

Mylotarg (gemtuzumab ozogamicin) has recently been authorised and 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).

The COMP also took 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 adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). 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. Taking into consideration the ESMO guideline and the authorisation status of medicinal products in AML, it was considered that significant benefit would need to be established versus standard induction chemotherapy consisting of anthracyclines and cytarabine. It was acknowledged that Vyxeos is authorised to substitute the traditional standard induction chemotherapy with daunorubicin and cytarabine without reference to other therapies that are used in combination in the first line. A demonstration of significant benefit over midostaurin (Rydapt) and gemtuzumab ozogamicin (Mylotarg), which are currently authorised to be used in combination with traditional induction chemotherapy, was therefore not required. Furthermore, significant benefit over first line therapies in non-intensive treatments and treatments authorised in the relapsed/refractory setting was not deemed necessay.

Significant benefit versus the induction therapy anthracycline (daunorubicin) and cytarabine (Ara-C) was supported by data collected from clinical trial CLTR0310-301. This clinical trial was assessed as pivotal evidence by the CHMP (please also refer to the EPAR of Vyxeos). It was a phase III, multicenter, randomised trial of Vyxeos liposome injection (also called CPX-351) versus cytarabine and daunorubicin in patients 60 -75 years of age with untreated high risk (secondary) AML study. The primary objective was to confirm the efficacy of Vyxeos compared with 7+3 as first line therapy in elderly patients (60 to 75 years old) with high risk (secondary) AML with the primary endpoint overall survival (OS) defined as the time from randomisation to death from any cause. Both arms in the

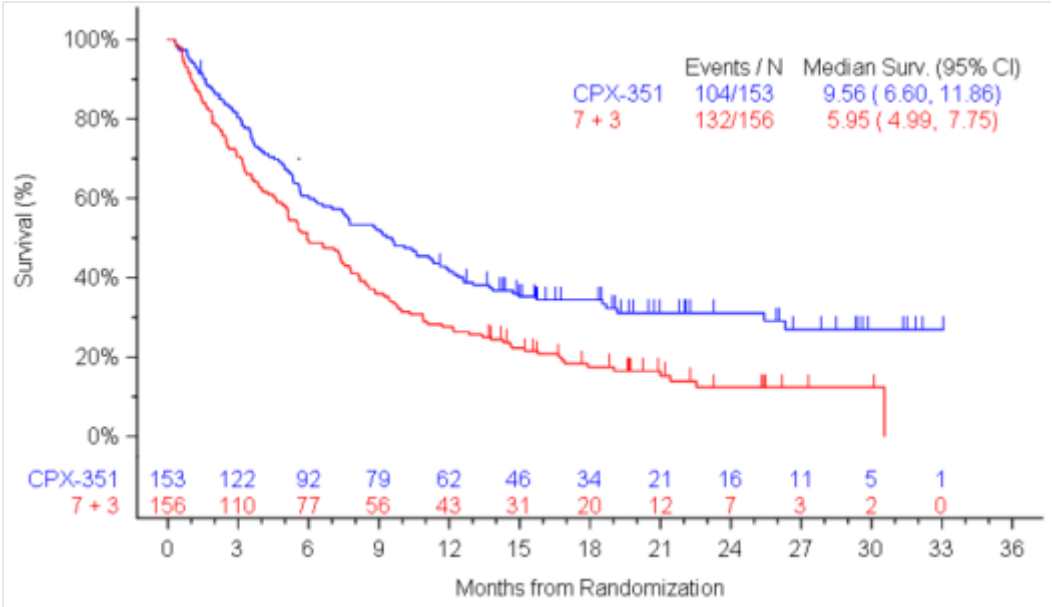
pivotal study were balanced with regards to baseline demography and disease characteristics. A significant improvement of 3.6 months in OS with Vyxeos compared to the 7+3 standard treatment has been demonstrated in the ITT population (figure 1 and table 3, median OS 9.56 months vs 5.95 months; HR = 0.69, 95% CI : 0.52 to 0.90, 1-sided p = 0.003). The CHMP deemed this to be a clinically relevant effect.

Table 3. Overall Survival (ITT Analysis Population-Study CLTR0310-301)

	CPX-351 (N=153)	7 + 3 (N=156)
Survived	49 (32.0)	24 (15.4)
Median Survival in Months (95% Conf. Int.)	9.56 (6.60, 11.86)	5.95 (4.99, 7.75)
Hazard Ratio (95% Conf. Int.)	0.69 (0.52, 0.90)	
p-value (1-sided)	0.003	

Note: P-value from stratified log-rank test
Note: Hazard ratio are calculated with the 7 + 3 arm as the reference group.

Figure 1. Kaplan-Meier Curve for overall survival (ITT population- Study CLTR0310-301)



The number and percentage of subjects transferred for HSCT after induction were measured as secondary endpoint. More patients in the Vyxeos treatment group received a HSCT in CR or CRi compared with patients in CR or CRi for the 7+3 regimen (table 4, 54.8% vs. 46.2%, respectively). A Kaplan-Meier analysis of the 91 subjects who received a transplant landmarked at the time of transplant showed that subjects in the Vyxeos group performed better than those in the control (HR=0.46, p = 0.009 [1-sided]). The median survival was not reached in the Vyxeos treatment group, whereas the median survival in the 7+3 treatment group was 10.25 months.

Table 4. Transplant Rate (Study CLTR0310-301)

	CPX-351 N = 153		7 + 3 N = 156
CR, n (%)	**57 (37.3)**		**40 (25.6)**
Received Transplant	30 (52.6)		19 (47.5)
No Transplant	27 (47.4)		21 (52.5)
CRi, n (%)	**16 (10.5)**		**12 (7.7)**
Received Transplant	10 (62.5)		5 (41.7)
No Transplant	6 (37.5)		7 (58.3)
Transplant rate	**52 (34.0)**		**39 (25.0)**
Odds ratio (95% CI)		1.54 (0.92, 2.56)	
p-value[a]		0.049 [a]; 0.097[b]	

Abbreviations: CI = confidence interval.

[a] 1-sided p-value is from a comparison of rates between treatment arms and is based on the Mantel-Haenszel test stratifying by age and AML type.

[b] 2-sided p-value is from a comparison of rates between treatment arms and is based on the Mantel-Haenszel test stratifying by age and AML type.

Taking into consideration the clinical data submitted to the COMP and the CHMP assessment of the benefit-risk, the COMP established significant benefit of Vyxeos based on a clinically relevant advantage over current standard '3+7' chemotherapy induction chemotherapy regimen with cytarabine and daunorubicin.

4. COMP position adopted on 02 July 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 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, Vyxeos is of significant benefit to adults with high-risk acute myeloid leukaemia as defined by therapy-related AML or AML with myelodysplasia-related changes. It was demonstrated that treatment with Vyxeos led to improved overall survival when compared to the currently authorised induction chemotherapy with daunorubicin and cytarabine which is standard of care treatment in newly diagnosed patients. There was also an increased rate of haematopoietic stem cell transplantation observed, which has curative potential. The Committee concluded that this constitutes a clinically relevant advantage.

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 Vyxeos, liposomal combination of cytarabine and daunorubicin, daunorubicin / cytarabine, EU/3/11/942 for treatment of acute myeloid leukaemia is not removed from the Community Register of Orphan Medicinal Products.