PRO CLAIMS IN ORPHAN MEDICINES APPROVED BY THE EUROPEAN MEDICINES AGENCY (EMA) FOR THE TREATMENT OF LYMPHOPROLIFERATIVE DISORDERS

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Background and Objectives

- Patient-Reported Outcome (PRO) assessments are based on a report that comes directly from the patient (i.e., study subject) about the status of particular aspects of or events related to a patient's health condition, without interpretation of the response by clinicians or anyone else. PROs include symptoms/signs, function, and quality of life but, in some contexts, they may also include satisfaction with care and adherence. PRO endpoints have gained a significant role in the medicine-approval process [1,2]. Guidance describing how regulatory bodies review and evaluate PRO instruments used to support claims in approved medical product labeling was issued by the EMA in 2005 [3] and the FDA in 2009 [4].
- Lymphoproliferative disorders are a group of diseases resulting from the abnormal proliferation of lymphocytes (B-and T-cells). They include lymphomas (Hodgkin and Non-Hodgkin), lymphoid leukemias, multiple myeloma, and Waldenstrom's macroglobulinemia.
- **The objectives of our study were:**
  - (1) To identify orphan medicines indicated for lymphoproliferative disorders approved by the European Medicines Agency (EMA)
  - (2) To identify medicines for which a PRO evaluation was performed
  - (3) To list those with a PRO labeling claim, and
  - (4) To identify reasons for not granting a PRO claim.

1. Marquis P, Caron M, Emery MP, Scott JA, Arnould B, Acquadro C. The role of health-related quality of life data in the drug approval processes in the US and Europe – A review of guidance documents and authorizations of medicinal products from 2006 to 2010. *Pharm Med* 2011; 25(3): 147-160.
2. Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. *Control Clin Trials* 2004;25:535-52.
3. European Medicines Agency. EMEA/CHMP/EWP/139391/2004. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. London, 27 July 2005.
4. U.S. Department of Health and Human Services, Food and Drug Administration. Patient-reported outcome measures: use in medical product development to support labeling claims. *Federal Register* 2009;74(35):65132-133.

Methods

- The search was performed on the EMA website (06/21/2014). The products were browsed by type (i.e., orphan medicines). Products refused and withdrawn were excluded.
- The PROLabels database was searched for each product retrieved to identify any PRO claim in the label. Summary of Product Characteristics (SmPC) and CHMP Assessment Reports (AR) were retrieved for each product and analyzed to find out about PRO evaluation reported in the AR and not reported in the label.

Results

- A total of 84 orphan medicines was identified on the EMA website, of which seven were refused and two were withdrawn. Of the 75 authorized, **thirteen orphan medicines indicated in lymphoproliferative disorders were identified**, representing three main indications: lymphomas (Hodgkin, systemic anaplastic large cell, T-cell lymphoblastic, mantle-cell), leukemias (chronic lymphocytic, hairy cell, acute lymphoblastic) and multiple myeloma. See Table 1.
- PRO evaluation (see Tables 1 and 2):
  - For ten products, no PRO assessement was performed at all.
  - Only one product had a PRO claim: ofatumumab (i.e., improvements associated with constitutional symptoms).
  - The label of another product (brentuximab vedotin) indicated "resolution of B symptoms." However, there was no clear mention in the AR on how the symptoms were collected (PRO measure? ClinRO measure?).
  - For one product (pomalidomide), a HRQL evaluation was mentioned in the AR, but not reported in the label. However, there was no detailed information about this evaluation in the AR. The reader is left to wonder about the HRQL results and the reasons for not including them in the label.

Table 1. Orphan medicines approved by the EMA for the treatment of lymphoproliferative disorders

Medicine Name	Product Number	Common name	MAH	Date of MA	Indication	PRO claim in SmPC	PRO evaluation in AR
Adcetris	EMEA/H/C/002455	brentuximab vedotin	Takeda Pharma	25/10/12	CD30+ Hodgkin lymphoma Systemic anaplastic large-cell lymphoma	**Not clear**	**Not clear**
Arzerra	EMEA/H/C/001131	ofatumumab	Glaxo Group	19/04/10	Chronic lymphocytic leukemia	**Yes**	**Yes**
Atriance	EMEA/H/C/000752	nelarabine	Glaxo Group	22/08/07	T-cell acute lymphoblastic leukemia T-cell lymphoblastic lymphoma	No	None
Evoltra	EMEA/H/C/000613	clofarabine	Genzyme Europe	29/05/06	Acute lymphoblastic leukemia in pediatric patients	No	None
Iclusig	EMEA/H/C/002695	ponatinib	Ariad Pharma	01/07/13	Ph+ acute lymphoblastic leukemia	No	None
Imnovid	EMEA/H/C/002682	pomalidomide	Celgene Europe	05/08/13	Multiple myeloma	**No**	**Yes**
Litak	EMEA/H/C/000504	cladribine	Lipomed	14/04/04	Hairy-cell leukemia.	No	None
Mozobil	EMEA/H/C/001030	plerixafor	Genzyme Europe	31/07/09	Lymphoma Multiple myeloma	No	None
Revlimid	EMEA/H/C/000717	lenalidomide	Celgene Europe	14/06/07	Multiple myeloma	No	None
Sprycel	EMEA/H/C/000709	dasatinib	BMS Pharma EEIG	20/11/2006	Ph+ acute lymphoblastic leukemia	No	None
Thalidomide Celgene	EMEA/H/C/000823	thalidomide	Celgene Europe	16/04/2008	Multiple myeloma	No	None
Torisel	EMEA/H/C/000799	temsirolimus	Pfizer	19/11/2007	Mantle-cell lymphoma	No	None
Xaluprine	EMEA/H/C/002022	6-mercaptopurine monohydrate	Nova Laboratories	09/03/2012	Acute lymphoblastic leukemia	No	None

Table 2. Orphan medicines approved by the EMA for the treatment of lymphoproliferative disorders with a PRO evaluation in the AR

Common name	Indication	Extract from the Sumamry of Product Characteristics (SmPC - section 5.1.) / in red, poster authors' comments	Extract from the CHMP Assessment Report (AR) / in red, poster authors' comments
brentuximab vedotin	CD30+ Hodgkin lymphoma Systemic anaplastic large-cell lymphoma (sALCL).	**P13 of the SmPC** Hodgkin Lymphoma: Of the 35 patients (33%) who had B symptoms at baseline, 27 patients (77%) experienced **resolution of all B symptoms** at a median time of 0.7 months from initiation of brentuximab vedotin. **P14 of the SmPC** sALCL: Of the 17 patients (29%) who had B symptoms at baseline, 14 patients (82%) experienced **resolution of all B symptoms** in a median time from initiation of brentuximab vedotin of 0.7 months.	***Outcomes/endpoints (p48/102)*** B-symptom resolution was defined as the proportion of patients with lymphoma-related B symptom(s) at baseline who achieve resolution of all B symptoms at any time during the treatment period. B symptoms were defined as fever, night sweats, or weight loss >10%. Comment: it is not reported how symptoms were collected (PRO? ClinRO?).
ofatumumab	Chronic lymphocytic leukaemia	**P 10 of the SmPC** Improvements also were demonstrated in components of the NCIWG response criteria. These included **improvements associated with constitutional symptoms**, lymphadenopathy, organomegaly, or cytopenias (see Table 2). (p 10 of the SmpC)	**Hx-CD20-406 / Secondary: Constitutional symptoms (p40/63)** **Constitutional symptoms were reported by subjects** and results captured by investigators every 4 weeks during the treatment period (Week 0 to Week 24) and through the follow-up period (Week 28 to Month 24) as part of assessment of response. More than three-quarters of subjects with baseline constitutional symptoms experienced complete resolution of all symptoms at some point during the study (79%, 61/77). All but one of these subjects experienced complete resolution during the treatment period. Nearly all responders with baseline constitutional symptoms experienced complete resolution (93%, 40/43). In addition, all subjects without constitutional symptoms at baseline remained symptom-free during the study.
pomalidomide	Multiple myeloma	Comment: No PRO claim in SmPC.	**Outcomes/endpoints – Secondary endpoints (p35/87)** Secondary endpoints included […] QoL (EORTC QLQ-MY20 and QLQ-C30). Comment: no results about HRQL evaluation were reported in AR.

Conclusions

- The percentage of PRO claims in orphan medicines approved by the EMA for lymphoproliferative disorders (7.7%) is inferior to the percentage of PRO claims in all EMA products (22%)[1]. This is remarkably low considering the profound effect of lymphoproliferative disorders on a patient's life.
- In addition, efforts should be made to improve the reporting of PRO data in the CHMP Assessment Reports.

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