Patient-Reported Outcome (PRO) Claims in Products Approved For Chronic Obstructive Pulmonary Disease (COPD) in Europe and the USA

Martine Caron, Laure-Lou Perrier , Catherine Acquadro
Mapi Research Trust, Lyon, France

Objectives

- The objectives of the study were:
  (1) To identify COPD products approved with a patient-reported outcome (PRO) labeling claim in Europe and the USA; and
  (2) to list the differences found in Europe vs. the USA in terms of products and labeling.

Methods

- The search was performed on:
  - the PROLabels database using the key word “pulmonary disease, chronic obstructive,
  - and the FDA- and EMA-approved medicinal product labels and medical reviews/scientific discussions (from January 1995 to February 2013 inclusive).

Results

- A total of 25 COPD products were retrieved (see Table 1):
  - 11 were approved by the EMA,
  - 14 by the FDA,
  - Only three INN were approved by both agencies: aclidinium bromide, indacaterol, and roflumilast, representing 11 products (EMA, n=8; FDA, n=3).

- Out of the 25 products approved, 15 have a PRO claim (EMA, n=8; FDA, n=7). See Table 1.

- When focusing on the INN approved by both agencies, the review showed that the FDA and the EMA agreed on the granting of a PRO claim (i.e., “yes” for aclidinium bromide and indacaterol, and “no” for roflumilast). The FDA and the EMA reviewed the same clinical studies. However, the labeling text differs between the agencies:

  - The FDA label of aclidinium bromide does not provide any mention of results measured by the St. George’s Respiratory Questionnaire (SGRQ) and the Transition Dyspnoea Index (TDI), while the EMA label does.
  - As for indacaterol, the FDA label does not mention any TDI results, while the EMA label does.
  - Reasons for these discrepancies are found in the FDA medical reviews. The TDI has been assessed as inadequate for use as a CT endpoint. As for the SGRQ, the results met the threshold of clinically meaningful improvement in only one study (see Table 2).

Table 1. PRO claims in COPD products approved by the EMA and the FDA (January 1995 to February 2013)

Reference Number(s)	Agency	INN	Brand Name	MAH	Date of Approval	PRO claim	
EMEA/H/C/002211	EMA	aclidinium bromide	Eklira Genuair	Almirall	20/07/2012	Yes	Eklira Genuair **provided clinically meaningful improvements in breathlessness (assessed using the Transition Dyspnoea Index [TDI]) and disease-specific health status (assessed using the St. George’s Respiratory Questionnaire [SGRQ]).** […] Patients treated with Eklira Genuair required less rescue medication than patients treated with placebo (a reduction of 0.95 puffs per day at 6 months [p=0.005]). Eklira Genuair also improved daily symptoms of COPD (dyspnoea, cough and sputum production) and night-time and early morning symptoms.)
EMEA/H/C/002706	EMA	aclidinium bromide	Bretaris Genuair	Almirall	20/07/2012	Yes	Idem Eklira Genuair
NDA 202450	FDA	aclidinium bromide	Tudorza Pressair	Forest Laboratories	23/07/2012	Yes	In Trials B and D but not in Trial C, patients treated with TUDORZA PRESSAIR used less daily rescue albuterol during the trial compared to patients treated with placebo.
NDA 021912	FDA	arformoterol tartrate	Brovana	Sunovion Pharma	06/10/2006	No	
NDA 021929	FDA	budesonide - formoterol fumarate dihydrate	Symbicort	AstraZeneca	21/07/2006	Yes	In both Studies 1 and 2, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of SYMBICORT 160/4.5.
NDA 021077	FDA	fluticasone propionate - salmeterol xinafoate	Advair Diskus	GlaxoSmithKline	24/08/2000	Yes	In both studies, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], p<0.001) in the first study and (30.4% reduction [95% CI: 16.9, 41.7], p<0.001) in the second study. Patients treated with ADVAIR DISKUS 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with patients treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], p <0.001) in the first study, and (34.3% reduction [95% CI: 18.6, 47.0], p<0.001) in the second study. Secondary endpoints including pulmonary function and symptom scores improved more in patients treated with ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both studies.
NDA 020831 - NDA 021279	FDA	formoterol fumarate	Foradil Aerolizer	Novartis	16/02/2001	Yes	In both pivotal trials compared with placebo, patients treated with FORADIL AEROLIZER 12 µg demonstrated improved morning pre-medication peak expiratory flow rates and took fewer puffs of rescue albuterol.
NDA 022007	FDA	formoterol fumarate	Perforomist	Mylan	27/04/2007	Yes	Patients treated with PERFOROMIST Inhalation Solution used less rescue albuterol during the trial compared to patients treated with placebo.
EMEA/H/C/002691	EMA	glycopyrronium bromide	Enurev Breezhaler	Novartis	28/10/2012	Yes	Symptomatic outcomes: [...] **Enurev Breezhaler once daily has also shown a statistically significant effect on health-related quality of life measured using the St. George’s Respiratory Questionnaire (SGRQ).** A pooled analysis of the 6- and 12-month pivotal studies found a statistically significantly higher percentage of patients receiving Enurev Breezhaler responded with a 4 point or greater improvement in SGRQ compared to placebo at week 26 (57.8% and 47.6% respectively, p<0.001). For patients receiving tiotropium, 61.0% responded with a 4 point or greater improvement in SGRQ (p=0.004 compared to placebo).
							[...] Other effects: Enurev Breezhaler once daily statistically significantly reduced the use of rescue medication (salbutamol) by 0.46 puffs per day (p=0.005) over 26 weeks and by 0.37 puffs per day (p=0.039) over 52 weeks, compared to placebo for the 6- and 12-month studies, respectively.
EMEA/H/C/002430	EMA	glycopyrronium bromide	Seebri Breezhaler	Novartis	28/09/2012	Yes	Idem Enurev
EMEA/H/C/002690	EMA	glycopyrronium bromide	Tovanor Breezhaler	Novartis	28/09/2012	Yes	Idem Enurev
EMEA/H/C/001211	EMA	indacaterol	Hirobriz Breezhaler	Novartis	30/11/2009	Yes	Symptomatic benefits: **Both doses demonstrated statistically significant improvements in symptom relief over placebo for dyspnoea and health status (as evaluated by Transitional Dyspnoea Index [TDI] and St. George’s Respiratory Questionnaire [SGRQ], respectively).** The magnitude of response was generally greater than seen with active comparators (Table 2). In addition, patients treated with Hirobriz Breezhaler required significantly less rescue medication, had more days when no rescue medication was needed compared to placebo and had a significantly improved percentage of days with no daytime symptoms. Pooled efficacy analysis over 6 months’ treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparison compared to placebo showed a ratio of rates of 0.68 (95% CI [0.47, 0.98]; p-value 0.036) and 0.74 (95% CI [0.56, 0.96]; p-value 0.026) for 150 microgram and 300 microgram, respectively.
EMEA/H/C/001114	EMA	indacaterol	Onbrez Breezhaler	Novartis	30/11/2009	Yes	Idem Hirobriz
EMEA/H/C/001210	EMA	indacaterol	Oslif Breezhaler	Novartis	30/11/2009	Yes	Idem Hirobriz
NDA 022383	FDA	indacaterol	Arcapta	Novartis	01/07/2011	Yes	In both COPD clinical trials including the 75 mcg dose (Trials 4 and 5), patients treated with ARCAPTA NEOHALER used less daily rescue albuterol during the trial compared to patients treated with placebo. **At week 12, pooled data from these trials demonstrated an improvement over placebo in SGRQ total score** of -3.8 with a 95% CI of (-5.3, -2.3) for the ARCAPTA NEOHALER 75 mcg dose, -4.6 with a 95% CI of (-5.5, -3.6) for 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) for 300 mcg. The confidence intervals for this change are widely overlapping with no dose ordering. Results from individual studies were variable, but is generally consistent with the pooled data results.
NDA 021527	FDA	ipratropium bromide	Atrovent HFA	Boehringer Ingelheim	17/11/2004	No	
NDA 020291	FDA	ipratropium bromide - albuterol sulfate	Combivent	Boehringer Ingelheim	24/10/1996	No	
NDA 020950	FDA	ipratropium bromide - albuterol sulfate	DuoNeb	Dey Labs	21/03/2001	No	
NDA 21747	FDA	ipratropium bromide - albuterol sulfate	Combivent Respimat	Boehringer Ingelheim	07/10/2011	No	
EMEA/H/C/001179	EMA	roflumilast	Daxas	Nycomed	05/07/2010	No	
EMEA/H/C/002398	EMA	roflumilast	Daliresp	Nycomed	28/02/2011	No	
EMEA/H/C/002399	EMA	roflumilast	Libertek	Nycomed	28/02/2011	No	
NDA 022522	FDA	roflumilast	Daliresp	Forest Laboratories	28/02/2011	No	
NDA 020692	FDA	salmeterol xinafoate	Serevent	GlaxoSmithKline	19/09/1997	No	
NDA 021395	FDA	tiotropium bromide	Spiriva Handihaler	Boehringer Ingelheim	30/01/2004	Yes	Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking Spiriva had a reduced requirement for the use of rescue short-acting beta2-agonists. Reduction in the use of rescue short-acting beta2-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

Table 2. Extracts from the FDA Medical Review of Turdoza Pressair (aclidinium bromide)

SGRQ	BDI/TDI
Disease-specific health-related quality of life was assessed in the aclidinium clinical development program using the St. George’s Respiratory Questionnaire. Health-related quality-of-life instruments are described as one of the commonly used secondary endpoints in the Agency’s Draft Guidance,[29] and there is regulatory precedent for labeling claims based on the SGRQ.[30] Results for the Applicant’s analysis of change in SGRQ total score are provided in Table 21 (Mean Change) and Table 22 (Proportions of Patients with Clinically Meaningful Improvement). A change in SGRQ total score of 4 units or greater was considered to represent a clinically meaningful improvement. Results for the treatment difference for mean change in SGRQ Total Score between the aclidinium 400µg and placebo groups are statistically significant for two of the three efficacy and safety trials (LAS-MD-33 and M/34273/34), but meet the threshold for clinically meaningful improvement in only one of the trials (M/34273/34). In each of the three trials, a numerically greater proportion of patients in the aclidinium 400µg treatment group experienced a clinically meaningful change in SGRQ Total Score as compared to placebo, however, the comparison of proportions was statistically significant only for Trial M/34273/34.	Results for the Applicant’s analysis of mean change in Translation Dyspnea Index focal score are provided in Table 23. The aclidinium clinical development program proposed a 1-unit increase as the threshold for a minimum clinically important difference. As noted in section 3.3, the Agency has not previously accepted the BDI/TDI as a validated measure of dyspnea, and the limitations of these instruments, including concerns about the validity of the 1-unit threshold for MCID, have been discussed in a prior Advisory Committee meeting.[31] Results for the treatment difference for mean change in TDI Focal Score between the aclidinium 400µg and placebo groups are statistically significant in all three effcicacy and safety trials, but meet the Applicant’s threshold for clinically meaningful improvement in only two of the three trials (LAS-MD-33 and LAS-MD-38 Part A). In none of the three trials do the effect sizes for the aclidinium 200µg treatment arm meet the Applicant’s 1.0 threshold. Again, it is noted that the BDI/TDI, while useful in a clinical setting, has been assessed as inadequate for use as a clinical trial endpoint from a regulatory standpoint[32], and there is no regulatory precedent for labeling claims based on the BDI/TDI.

Conclusion

- Our review showed that PROs are often included in COPD product labels in Europe and in the USA.
- Although the FDA and the EMA agree on a general level, the FDA seems more restrictive in the label wording.

For more information, please contact:
Martine Caron, mcaron@mapigroup.com
www.mapigroup.com

Mapi Research Trust

ISPOR 16th Annual European Congress - November 2013