EPV-504

Cost-analysis of the tolerability, adherence and persistence to treatment of diroximel fumarate versus dimethyl fumarate

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OBJECTIVE

- To compare the economic impact of tolerability profile, adherence, persistence and productivity loss of diroximel fumarate (DRF) versus dimethyl fumarate (DMF) in the treatment of patients with multiple sclerosis (MS) in Spain.

CONCLUSIONS

- Considering the described parameters and the limitations on multiple sources used, DRF would be a cost saving alternative compared to DMF for MS patients.

European Academy of Neurology - 9th Congress | 1 - 4 Jul 2023

Introduction

- Diroximel fumarate (DRF) [Vumerity®] is a second-generation oral fumarate for the treatment of relapsing remitting multiple sclerosis with an improved gastrointestinal (GI) tolerability profile compared to dimethyl fumarate (DMF) [Tecfidera®] treatment, as reported in the phase III EVOLVE-MS-2 study.[1] In addition, DRF patients reported lower impact on work productivity loss associated with GI adverse events (AEs) than DMF patients.[2]
- Adherence and persistence in MS patients affects clinical outcomes, such as disease progression and relapse frequency, as well as economic impact.[3] The proportion of days covered (PDC), is a common criteria for estimating adherence in MS, defines as PDC ≥ 80.0%.[3] Adherent MS patients had 53% fewer hospitalisations and 38% fewer emergency department visits.[3]
- Therapeutic persistence is essential to maximise treatment outcomes, especially in chronic diseases such as MS.[4] In the long-term, persistence can measure the rate of treatment discontinuation, which is usually not the same as observed in clinical trials.[4] Higher persistence to MS treatment may lead to delay in the use of second-line drug-modifying therapy (2L DMT) which often incurs a higher pharmaceutical cost and early run out of therapeutic opportunities.[5,6]

Methods

Model design

- A cost analysis model was designed to evaluate tolerability profile, treatment adherence, treatment persistence (healthcare direct costs) and lost productivity (indirect cost) of DRF versus DMF treatments over an annual time horizon.

Approach and clinical data

- The cost of tolerability was calculated using the probability of occurrence of AEs (based on the tolerability profile) and the cost of managing each AE. Tolerability profile was derived from a direct comparison of DRF versus DMF (EVOLVE-MS-2 study) that reported mean rates of GI AEs (34.8% vs. 48.2%)[1,2] and flushing (45.8% vs. 55.0%)[7] (Table 1).
- The adherence profile estimated the difference of MS relapse (annualised relapse rate, ARR) cost between adherent and non-adherent patients. Adherence rates (PDC ≥ 80.0%) considered were extracted from real-world evidence (RWE) (DRF: 85.0%, DMF: 60.0%)[8]. ARR data were selected from the phase III clinical studies, EVOLVE-MS-1 (DRF: 0.16)[9] and ENDORSE (DMF: 0.20)[10], and assumed as valid values for adherent patients. Subsequently, a lower ARR (42%)[3] was assumed in adherent patients than in non-adherent patients (Table 1).
- Persistence cost included DRF and DMF acquisition cost according treatment persistence, plus 2L treatment costs. An extrapolation of RWE data[11,12] was used to calculate persistence in the first year (DRF: 10.8 months; DMF: 8.4 months). Switching to 2L with DMTs (natalizumab, fingolimod, alemtuzumab, cladribine, ocrelizumab) was assumed after DRF or DMF discontinuation. 2L DMTs acquisition and intravenous (IV) administration (when required) costs were calculated and applied for the remainder of the time horizon (up to 12 months) (Table 1). Results from a market research analysis of the switch from DMF to 2L were used for the proportion of 2L treatments.
- The cost of work productivity loss related to GI AE per year was estimated by considering lost productivity time and labour cost. Productivity loss (DRF: 9.5h; DMF: 18.7h) was calculated based on the average number of working hours missed (DRF: 4.3; DMF: 5.5)[2] and the average number of days of absence with a minimum of 1 hour lost (DRF: 2.2; DMF: 3.4)[2] (Table 1).

Cost

- Costs are expressed in euros, at 2022 values (€, 2022).
- Reimbursed drug ex-factory prices (DMF[g], 2L DMT[g], and DRF confidencial data), and IV administration cost (€205.55)[14] were used for drug-acquisition cost estimation.
- Unitary costs for GI AEs management were €948.48 (diarrhoea), €499.55 (nausea), €789.78 (abdominal pain) and €921.31 (vomiting).[14] Moreover, flushing management cost included a specialist visit (€148.75)[14] and the drug cost treatment for the event (€1.00)[6,14].
- An average relapse event cost (€1,302.48)[15] was used to calculate the cost of adherence.
- The standard labour cost (€16.35/hour)[16] at the Spanish setting was considered.

Table 1. Parameters considered in the cost-analysis

Parameters	Diroximel fumarate (DRF)	Dimethyl fumarate (DMF)
EA GI[a]	34.8%[1,2]	48.2%[1,2]
Diarrhoea	15.4%[1,2]	22.3%[1,2]
Nausea	14.6%[1,2]	20.7%[1,2]
Upper abdominal pain[b]	6.7%[1,2]	15.5%[1,2]
Abdominal pain[b]	6.3%[1,2]	9.6%[1,2]
Lower abdominal pain[b]	5.9%[1,2]	6.8%[1,2]
Vomiting	3.6%[1,2]	8.8%[1,2]
Any flushing or flushing-related EA[a]	45.8%[7]	55.0%[7]
Adherence		
Adherent[c] / non-adherent[d] proportion	85.0%[8] / 21.0%	60.0%[8] / 26.0%
Adherent[e] / non-adherent[f] ARR	0.16[9] / 0.28	0.20[10] / 0.34
Persistence, in months[g]	10.8	8.4
Productivity loss[a]		
Days with absence (≥1 hour)	2.2[2]	3.4[2]
Work hours missed (per day of absence)	4.3[2]	5.5[2]

a. Data obtained from direct comparison of DRF vs DMF in EVOLVE-MS-2.[1,2,7] b. Sum of all abdominal pain was applied. This could lead to overestimation, as the same patient could present pain at different levels; c. For adherence (defined as proportion of days covered, PDC ≥ 80%), the data was extracted from real-world adherence=rates[8]; d. Data obtained by calculation (100% - adherent patient %); e. Assumed valid ARR values for adherent patients. Data from clinical trials EVOLVE-MS-1[9] and ENDORSE[10]; f. Data obtained by calculation, applying 42% fewer relapses in non-adherent patients; g. Data calculated by extrapolation of curves from RWE studies (DRF: Acaria Health[11]; DMF: Biogen ONE[12]).

Results

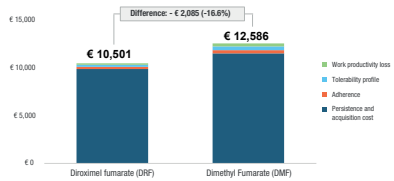
- The total annual cost per patient resulted in € 10,501.14 for DRF and € 12,586.04 for DMF (Table 2 and Figure 1). The difference between DRF and DMF would imply an annual cost reduction of 16.6%, in favour of DRF (Table 2 and Figure 1).
- DRF provided cost savings associated to acquisition cost and persistence (- € 1,642.90), enhanced tolerability profile (- € 186.01), better adherence (- € 104.92) and less impact on work productivity (- € 151.07) (Table 2).

Table 2. Annual costs of DRF vs. DMF, and differences

Parameters	Diroximel fumarate (DRF)	Dimethyl fumarate (DMF)	Absolute difference (DRF-DMF)	Proportional difference vs DMF
Persistence and drug cost acquisition[a]	€ 9,906.34	€ 11,549.23	- € 1,642.90	- 14.2%
Tolerability profile[b]	€ 209.10	€ 395.11	- € 186.01	- 47.1%
Adherence	€ 231.03	€ 335.95	- € 104.92	- 31.2%
Work productivity loss	€ 154.67	€ 305.75	- € 151.07	- 49.4%
Total	**€ 10,501.14**	**€ 12,586.04**	**- € 2,049.44**	**- 16.6%**

a. Drug-acquisition cost of DRF or DMF during months of persistence, plus 2L DMTs cost up to one year of treatment.
b. Management cost of GI AEs and flushing.

Figure 1. Annual cost per patient



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