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The Cost-effectiveness of Sativex®: The Italian Experience Based on "Sativex in Resistant Multiple Sclerosis Spasticity: Discontinuation Study in a Large Population of Italian Patients, SA.FE. Study"

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Spasticity is a common, worsening and disabling symptom of MS [1,2]. Severe to moderate spasticity is present in approximately 30-40% of patients with a 10-year history of MS and the proportion increases along with disease duration [1,3,4].

Recently, Sativex® oromucosal spray, a 1:1 mixture of 9-d-tetrahydocannabinol and cannabidiol, is available in many EU countries as add-on therapy for adult MS patients with moderate to severe spasticity not adequately responding to first-line antispastic medications [5,6]. The efficacy and safety of Sativex® in treatment-resistant spasticity have been demonstrated in randomized controlled trials, observational studies and post-marketing safety studies [7-11].

In Italy the Agenzia Italiana del Farmaco (AIFA) prescribing instructions stipulated that an improvement of at least 20% from the baseline in spasticity 0-10 numerical rating scale (NRS) scores, must be achieved within the first 4 weeks of use of Sativex® to continue its prescription. In the largest multicentre Italian study evaluating the efficacy and safety of Sativex®, 70.5% of MS patients were considered as responders according to the AIFA labeled criteria [12]. Moreover, in this population about 40% discontinued treatment: 26.2% interrupted because of lack of effectiveness and 18.7% for adverse events [12].

Thus, in order to study Sativex® discontinuation and safety profile in this large population of Italian MS patients, we analyzed discontinuation time for lack of efficacy, considering the outcome-based risk and cost sharing Italian agreement time frames (4 weeks and 6 weeks) [13]. In this study, the Kaplan-Meier survival curve, in the overall group of discontinuing patients, 20.8% patients discontinued treatment after 4 weeks while 26.4% discontinued after 6 weeks. Moreover, we found after adjusted modeling that the NRS score at T1 visit was predictive of treatment discontinuation, suggesting that the 4 weeks trial is effective in identifying those patients where Sativex® could be effective, thus limiting the economic burden of Sativex® on the health system.

Indeed, in addition to clinical effectiveness, the Sativex® cost-effectiveness should also have been seriously considered for public reimbursement in many countries. In those EU countries that have approved Sativex® as an add-on strategy therapy, the relatively high cost of this drug and the uncertainty over the size and duration of benefits have emphasized the importance of economic evaluation to inform commissioning policy.

In particular, the cost-effectiveness of Sativex® has been addressed for the UK, German and Spanish settings, showing that the UK model resulted in an unfavorable incremental cost-effectiveness ratio (ICER), whilst analyses using the Spanish and German models concluded that Sativex® was cost-effective in these two countries [14,15].

In Italy, the reimbursement approach adopted by the Italian Medicines Agency for new medications is named Managed Entry Agreement (MEA). According to this response-based risk-sharing agreement, both payment by result (PbR) and cost sharing (CS) concepts are considered for Sativex® reimbursement. While the PbR consists of a complete reimburse of all early non-responder patients by the company (a 100% payback), the CS provides for a 50% of reimbursement for patients on treatment for 6 weeks [13]. In other words, the health system avoids the cost of early non-responders, being reimbursed if the outcome is not reached, thus saving resources.

Therefore, since the pharmaceutical company reimbursed 100% of the patients failing at 4 weeks and 50% of all patients reaching 6 weeks, the Italian Medicines Agency, in our MS population on Sativex® treatment, got fully reimbursed for the 20.4% patients not responding after 4 weeks and for 50% of those reaching 6 weeks, according to the PbR and CS methods [13].

In a recent pharmacoeconomic analysis, the base case ICER for Sativex® use in Italy over a 5 year period was €4,968 per quality-adjusted life-year gained (year of costing: 2013) [16]. Through a deterministic and probabilistic sensitivity analyses, this research demonstrated that Sativex® is an efficient cost-effective treatment option for patients with MS-related spasticity in the Italian healthcare context, remaining below the incremental threshold of €30,000 per quality-adjusted life-year gained [16].

In conclusion, bearing in mind that the MS spasticity can lead to worsening of other MS-related symptoms such as sleep disturbances, pain, and bladder dysfunction, impacting quality of life and health care cost, the Sativex® treatment in clinical responders MS patients could be able to improve patients' overall well-being by relieving these associated symptoms. Moreover, the utilization of appropriate therapeutic measures, such as physiotherapy, multidisciplinary specialists support and medications customized for each patient can also impact the treatment goal optimizing the costs.

Finally, the designation of such a clearly defined trial period and initial response threshold seems to be able to ensure the Sativex® prescription and use only for those patients exhibiting a clinically meaningful benefit allowing for a more rational use of resources.

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