Sativex® confirms clinically relevant benefits in Multiple Sclerosis Spasticity

- **Positive data from the MObility ImproVEments with Spasticity in Multiple Sclerosis (MOVE) 2 study, presented at ECTRIMS congress, supports the use of Sativex® to reduce symptoms of moderate to severe spasticity due to multiple sclerosis (MSS)**

- **The new study data shows that, after three months, 41% of patients treated with Sativex®, who were resistant to other therapies, showed a clinically relevant effect**

- **The medicine has proven to be a cost effective treatment in Germany, where Almirall has already made it available as well as in Spain and Denmark**

Lyon, France, 11th October 2012: Almirall S.A. (ALM) today announces that results of the MObility ImproVEments with Spasticity in Multiple Sclerosis (MOVE) 2 observational study performed in Germany, with 300 patients, showed that one month's treatment with Sativex® (THC:CBD) oromucosal spray reduces moderate to severe multiple sclerosis spasticity (MSS) by 20% or more in 4 out of 10 patients previously unresponsive to conventional therapies. After three months, the improvement observed was 30% or more. Overall, 55% of the initial patients were eligible for continuing treatment beyond the third month.

This prospective, observational study is presented today at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Lyon, France.

"An improvement on the numerical rating scale (NRS) of at least 30% after 3 months is considered clinically relevant. For patients, it translates into less disturbed sleep due to MSS spasms, less pain, improved bladder function and a greater ability to perform simple daily activities involving mobility. These findings from everyday clinical practice are aligned or superior to those reported in previous clinical trials with Sativex®, and were achieved with slightly fewer average daily doses," commented MOVE 2 lead investigator Professor Peter Flachenecker, Neurological Rehabilitation Centre Quellenhof, Bad Wildbad, Germany.

The MOVE 2 is a multicentre, prospective, observational study including 300 adults with moderate to severe MSS treated in 42 specialised MS centres throughout Germany. Mean MS spasticity NRS scores decreased by 25% compared to pre-treatment with Sativex®, with 41% of patients improving at least 30% from baseline (from 6.7 to 3.2 in this subgroup; $p<0.0001$). Quality of life measurements (MS QoL-54 scale) also improved from baseline in the third month's visit ($p<0.01$).

Sativex® was generally well tolerated. Adverse events were reported in 16.6% of the treated patients, being the most common ones dizziness, fatigue or drowsiness mostly transient and mild or moderate in intensity.

Other new data from Sativex® ongoing registries in the UK (n=493, retrospective data collection, 18 months mean exposure) and Spain (n=103, 6 months prospective follow-up) which are being presented in this congress, further support these findings.

On top of the clinical relevance demonstrated in the MOVE 2, a recent publication from J. Slof shows that Sativex® is a cost effective treatment[i]. In a Markov model[ii] from the German healthcare payer perspective, the incremental cost effectiveness ratio for Sativex® was €10,809. This is well below commonly accepted thresholds for cost effectiveness, such as the £30,000 (€38,000) specified by the UK National Institute for Health and Clinical Excellence (NICE).

In Europe, Sativex® is commercialized for the treatment of MS spasticity in the UK, Spain, Germany and Denmark. Launches are also currently in preparation in Italy, Austria, Iceland and Norway. In addition, regulatory authorization has been also received in Belgium, Sweden, the Netherlands, Portugal, Czech Republic and Slovakia with launches expected from the end of 2012 onwards.

In addition to MS spasticity, Sativex®, which has been developed by GW Pharmaceuticals, is also in phase III clinical development for the treatment of cancer pain. Almirall holds the marketing rights to this medicine in Europe (except the United Kingdom) and Mexico.

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Notes to Editors

About the MOVE2 study
MObility Impro**VE**ments with Spasticity in Multiple Sclerosis (MOVE) 2 was a multicentre, prospective, observational study including 335 adults (300 of which were analysable) with moderate to severe MSS treated in 42 specialised MS centres throughout Germany. The study was designed to evaluate the effectiveness of Sativex® during routine clinical practice. Patients were assessed at entry to the study, at one month and at three months, using validated instruments, including the NRS, the Barthel activities of daily living index and the Ashworth spasticity scale

After an initial one-month trial of treatment, in the effectiveness analysis population of 276 patients:

- 74.6% were considered initial responders to the treatment by their physicians
- 41.7% of patients' MS spasticity Numerical Ratings Scale (NRS) improved ≥ 20% compared to the score measured before they began Sativex treatment.
- The overall mean Ashworth spasticity score fell by 9.6% to 2.7 (SD 0.90), decreasing by 12.8% (to 2.6 (SD 0.9) in the subgroup of patients improving ≥ 20% on the NRS score.
- The mean sleep NRS score decreased by 21.4% from before patients began Sativex treatment, falling by 36% in patients improving ≥ 20% on their baseline score.
- Responders' evolution of spasticity associated symptoms comparisons p-values: pain 0.08, stiffness 0.01, bladder dysfunction 0.007, mobility 0.05.

237 (79%), of the 300 analysable patients included in the study, continued to take Sativex® after the initial trial of treatment. In these patients, the benefits seen after one month's treatment were maintained or improved at three months from baseline:

- Mean MSS Numerical Rating Scale (NRS) scores decreased by 25% compared to before they began Sativex treatment, with 41% of patients improving by at least 30% from baseline (from 6.7 to 3.2 in this subgroup; $p<0.0001$)

- Mean sleep NRS score decreased by 27% from baseline, (from 4.3 to 2.1; p<0.0001)
- Average dose used was 6.7 sprays/d (S.D 2.9) at the three months visit

At three months, the proportion of patients with MSS who needed physiotherapy home visits fell by one third from 27.3% to 17.8%. Severe limitations in activities of daily living were reported by 25% fewer patients, while the proportion of patients reporting severe and disturbing pain fell by 15.5%. Sativex® was generally well tolerated. Adverse effects type were similar to those reported in clinical trials, such as dizziness and drowsiness, but with fewer incidences. After the three-month visit, 55.3% of baseline patients continued to take Sativex®.

About Sativex®

Sativex® is an endocannabinoid modulator made of two actives - THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol)-, which was developed and is manufactured by GW Pharmaceuticals plc, UK. Almirall holds marketing rights in Europe (except United Kingdom) and Mexico.

Sativex® is indicated as a treatment for patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not adequately responded to other anti-spasticity medications and who have demonstrated a clinically significant improvement in symptoms related to spasticity during an initial treatment testing period[iii]. Sativex® is effective in all types of MS, independently of the disability status (as per Expanded Disability Status Scale –EDSS) a rating system that is frequently used for classifying and standardizing the condition of people with multiple sclerosis).[iv]

Sativex® contains active ingredients known as 'cannabinoids', which are extracted from the plant *C. Sativa* grown and processed under strictly controlled conditions. Cannabinoids react with cannabinoid receptors that exist naturally throughout our body, including the brain.[v] A receptor is a site located in a brain cell in which certain substances can stick or "bind" for a while. If this happens, this binding has an effect on the cell and the nerve impulses it produces, causing a 'dimming-down' of the spasticity symptom. In patients who respond to Sativex®, this is the effect that improves their spasticity symptoms and helps them cope with their daily activities.[vi]

In addition to MS spasticity, Sativex®, which has been developed by GW Pharmaceuticals, is also in phase III clinical development for the treatment of cancer pain.

Spasticity

In the five main EU markets there are around 500,000 people suffering from MS [vii]. Spasticity is a symptom defined by patients and carers as muscle spasms, seizing-up, stiffness and/or difficulty in moving muscles and it is one of the most common symptoms of MS, occurring in up to 75% of MS sufferers in the course of the disease. Spasticity can affect many aspects of the daily lives of patients with MS and is one of the main factors contributing to their distress and disability.[viii]

About Almirall

Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, it researches, develops, manufactures and commercialises its own R&D and licensed drugs with the aim of improving people's health and wellbeing. Almirall focuses its research resources on respiratory, gastrointestinal, dermatology and pain. Almirall's products are currently present in over 70 countries in the five continents. With the opening of the Canadian affiliate, Almirall has now direct presence in Europe, Mexico and Canada through 13 affiliates.
For further information please visit: www.almirall.com

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[i] Sativex® in multiple sclerosis spasticity: a cost-effectiveness model - Slof J et al, Expert Rev. Pharmacoecon. Outcomes 2 Res. 12(4), (2012))

[ii] Markov models in medical decision making: a practical guide. - Sonnenberg FA, Beck JR. - Med Decis Making. 1993 Oct-Dec;13(4):322-38.

[iii] Patient leaflet

[iv] *A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis* - Novotna A. et al, European Journal of Neurology 2011 – Sept ; 18(9):1122-31.

[v] GW Pharmaceuticals: Cannabinoid Science: Mechanism of action. Available at. http://www.gwpharm.com/mechanism-of-action.aspx (latest access: 26/04/2012).

[vi] GW Pharmaceuticals: Cannabinoid Science: Cannabinoid Compounds. Available at http://www.gwpharm.com/types-compounds.aspx (Last accessed: 26/04/12).

[vii] Multiple Sclerosis International Federation: European map of ms database. ©2010 EMSP, MSIF. Available at: www.europeanmapofms.org (latest access: 11/08/2010). *Top five EU countries include: France, Germany, Italy, Spain and UK.*

[viii] Rizzo MA *et al*. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult Scler* 2004;10:589–595.