Almirall announces regulatory filing of linaclotide for the treatment of irritable bowel syndrome with constipation in Europe

- **Linaclotide has demonstrated statistically significant improvement in abdominal pain/discomfort and global relief of IBS-C symptoms in Phase III clinical trials[1,2]**

- **IBS-C is a debilitating disease associated with reduced quality of life and considerable socio-economic and psychological consequences[3,4]**

Barcelona (Spain), 29th September 2011 - Almirall, S.A. (ALM.MC) announced today that it has submitted a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) for linaclotide, an investigational guanylate cyclase-C (GC-C) receptor agonist for the treatment of irritable bowel syndrome with constipation (IBS-C). Once approved, linaclotide will be marketed in Europe under the trademark Constella®.

"IBS is associated with significant reduction in quality of life and intensive consumption of healthcare resources. In particular, people suffering from IBS-C currently have very limited treatment options available to them. Patients and physicians are frustrated because of this lack of specific therapy for IBS-C", said Bertil Lindmark, Chief Scientific Officer at Almirall. *"The results of clinical trials are extremely encouraging and, with this regulatory submission of linaclotide in IBS-C, we look forward to bringing this novel first in class medicine to patients in Europe."*

The submission includes efficacy and safety data from a Phase III program comprising two double-blind placebo-controlled trials[1,2] and two open-label long term safety studies. A total of more than 1,600 subjects received an once-daily dose of either linaclotide or placebo across the two placebo-controlled studies in patients with IBS-C. Full results of these two studies will be presented at the European Gastroenterology Week (UEGW) congress in Stockholm in October 23rd-26th, 2011.

This MAA follows the submission of an NDA for linaclotide to the US Food and Drug Administration (FDA) in August 2011 by Ironwood Pharmaceuticals Inc. and its US partner, Forest Laboratories Inc.

Almirall licensed from Ironwood the rights to develop and commercialize linaclotide in Europe.

About the Phase III studies
The efficacy and safety of linaclotide in IBS-C has been evaluated in two large double-blind placebo-controlled Phase III studies.[1,2] In both trials, linaclotide was shown to be significantly superior to placebo for improving pain/discomfort, degree of relief, complete spontaneous bowel movement frequency, stool consistency, severity of straining and bloating. These improvements were sustained over the entire treatment periods (12 and 26 weeks). Diarrhoea was the most prevalent adverse event (linaclotide 20%, placebo 3%), mainly mild to moderate in intensity, that only led to discontinuation in 5% of linaclotide-treated patients.

About Linaclotide
Linaclotide, a first-in-class investigational drug, is an agonist of the guanylate cyclase type-C (GC-C) receptor located on the luminal surface of the intestine. In preclinical models, linaclotide reduced visceral hypersensitivity, increased fluid secretion, and accelerated intestinal transit. The effects on secretion and transit are mediated through cyclic guanosine monophosphate (cGMP), which is also believed to modulate the activity of local nerves to reduce pain. Linaclotide is an orally delivered

peptide that acts locally in the gut with no measurable systemic exposure at therapeutic doses and is intended for once-daily administration.

Ironwood Pharmaceuticals, Inc. and Forest Laboratories, Inc. are co-developing and, if approved, will co-promote linaclotide in the United States. Ironwood has out-licensed linaclotide to Almirall for European development and commercialisation and to Astellas Pharma Inc. for development and commercialisation in Japan, Indonesia, Korea, the Philippines, Taiwan and Thailand.

About Irritable Bowel Syndrome with Constipation (IBS-C)
IBS is defined as 'a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit and with features of disordered defecation'.[5]

The Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders includes criterion for the diagnosis of IBS,[6] as:

- Recurrent abdominal pain or discomfort at least three days/month, in the last three months, associated with two or more of the following:
  - ✓ improvement with defecation
  - ✓ onset associated with a change of frequency of stool
  - ✓ onset associated with a change in form (or appearance) of stool

The estimated prevalence of IBS at 10-15% of the European population puts it in line with higher profile conditions such as migraine (12%) and asthma (11%).[7] It leads to a substantial reduction in quality of life, accompanied by considerable socio-economic and psychological consequences[3,4] and represents a major proportion of gastrointestinal workload in both primary and secondary care[10].

Owing to the complex, multimodal nature of the condition there is no cure for IBS and no 'gold standard' of treatment.[8] Irritable bowel syndrome with constipation (IBS-C) is one of four clinically different subtypes of IBS. One third of patients with IBS are thought to have IBS-C, [4,5,9] and therefore live with both abdominal pain and constipation.

About Almirall
Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, Spain, 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 therapeutic areas related to the treatment of asthma, COPD (Chronic Obstructive Pulmonary Disease), gastrointestinal disorders, psoriasis and other dermatological conditions.

Almirall's products are currently present in over 70 countries while it has direct presence in Europe and Latin America through 12 affiliates.

For further information please visit the website at: www.almirall.com.

Almirall media contact:
Ketchum Pleon
+44 20 7611 3653
Amanda.sefton@ketchumpleon.com

References

[1] Rao S. et al. - Efficacy and Safety of Once Daily Linaclotide in Patients With Irritable Bowel Syndrome With Constipation: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial Followed by a 4-Week Randomized Withdrawal Period. Digestive Disease Week, May 7-10 2001, Chicago Abstract#: 845

[2] Chey, W. et al. - Efficacy and Safety of Once-Daily Linaclotide Administered Orally for 26 Weeks in Patients With IBS-C: Results From a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial. Digestive Disease Week, May 7-10 2001, Chicago Abstract#: 837

[3] Maxion-Bergemann S, Thielecke F, Abel F, Bergemann R. - Costs of irritable bowel syndrome in the UK and US. Pharmacoeconomics 2006;24:21–37

[4] Davis RH. - Overcoming barriers in irritable bowel syndrome with constipation (IBS-C). J Fam Pract 2009;58:S3–S7

[5] Longstreth GF, Thompson WG, Chey WD et al. - Functional Bowel Disorders. Gastroenterology 2006; 130: 1480-1491

[6] Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders

[7] P. S. Hungin et al - The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects - Aliment Pharmacol Ther 2003; 17: 643–650.

[8] Camilleri M, Chang L. - Challenges to the therapeutic pipeline for irritable bowel syndrome: end points and regulatory hurdles. *Gastroenterology* 2008;135:1877–1891

[9] American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; 104 Suppl 1:S1-35