Press Release

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Shire Receives Extension of Market Authorization in Europe for Revestive▼ (Teduglutide) for the Treatment of Paediatric Patients with Short Bowel Syndrome (SBS)

First therapy indicated in the EU for use in patients aged one year and above with SBS, a rare gastrointestinal condition

ZUG, Switzerland – July 7, 2016 – Shire (LSE: SHP, NASDAQ: SHPG) today announced that the European Commission has granted extension of Market Authorization for Revestive®* (teduglutide) 5 mg powder and solvent for solution for injection for the treatment of patients aged one year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

"We are very pleased to be able to bring Revestive, the first product indicated specifically to treat paediatric SBS patients in Europe," said Ueli Fankhauser, Head, Global Product Strategy. "This extension of EU Market Authorization for Revestive represents an important advance in the treatment of SBS in paediatric patients."

SBS is a rare gastrointestinal condition characterised by a clinically significant reduction in intestinal absorptive capacity as a consequence of surgical resection of large portions of the intestine, commonly due to congenital abnormalities, disease or trauma.

The European Commission decision to grant extension of Market Authorization for Revestive in the treatment of paediatric patients with SBS follows a positive opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) in May 2016.

Estimates of the prevalence of SBS with Intestinal Failure (SBS-IF) in children vary markedly, largely due to the lack of standardised reporting and rarity of the disease. In a recent cross-sectional study in the Netherlands (the nationwide DRIFT registry study), the prevalence of chronic IF requiring home parenteral support (PS) was 9.6 per million in children. In the DRIFT registry population, 43.2% of children with chronic IF had SBS, which translates into a Dutch national prevalence of paediatric SBS-IF requiring home parenteral nutrition of 4.1 per million.

Supportive Paediatric Data

A 12-week, open-label, multicentre, safety, pharmacokinetic and pharmacodynamic study was conducted in 42 children aged 1-17 years who had SBS-IF for at least one year and had plateaued in parenteral support (PS) reduction with minimal or no advance in enteral nutrition

for at least three months. Of the participants, 37 received teduglutide 0.05 mg/kg/day (n=15); 0.025 mg/kg/day (n=14); 0.0125 mg/kg/day (n=8); and five received standard of care.

Of the 42 patients, 40 (95%) completed the study. Most adverse events were related to gastrointestinal complaints and/or central line-related issues. No deaths were reported, no serious drug-related adverse events were observed, and no patient discontinued the study due to adverse events. No safety signals related to fluid overload, obstruction, hepatobiliary system, or colonic polyps were seen in the study.

Although the study was not powered for efficacy, the data showed that children treated with teduglutide 0.05 mg/kg/day and 0.025 mg/kg/day had reductions from baseline to week 12 in PS volume requirements, and increases from baseline in enteral nutrition volume. Four patients achieved independence from PS (three in the teduglutide 0.05 mg/kg/day group, one in the 0.025 mg/kg/day group). Despite PS reductions, clinical and nutritional status remained stable across the teduglutide treatment groups.

About Short Bowel Syndrome (SBS)

SBS is a rare and potentially life-threatening gastrointestinal condition. It is characterized by a clinically significant reduction in intestinal absorptive capacity as a consequence of surgical resection of large portions of the intestine commonly due to congenital abnormalities, disease or trauma. If intestinal adaptation is inadequate, the absorptive capacity of the residual intestine becomes insufficient to meet the nutritional, fluid and electrolyte needs to sustain the life and growth requirements of a child; this leads to IF, which requires chronic dependence on PS to maintain adequate growth, hydration, protein, electrolyte, and micronutrient balances. SBS is the most common cause of IF in the paediatric population.

About Revestive

Revestive contains the active substance teduglutide, a glucagon-like peptide-2 (GLP-2) analogue. It is indicated for the treatment of patients aged one year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery. It improves the absorption of nutrients and fluid from the remaining gastrointestinal tract and enhances key structural and functional adaptations in the intestinal mucosa.

Revestive received Market Authorization in Europe in 2012 for the treatment of adult patients with SBS, who should be stable following a period of intestinal adaptation after surgery. It is also currently indicated in Canada for the treatment of adult patients with SBS who are dependent on PS, and in the United States under the name GATTEX® (teduglutide [rDNA origin]) for injection for the treatment of adult patients with SBS who are dependent on PS.

Safety Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system found under section 4.8 of the SmPC.

Contraindications
Hypersensitivity to the active substance or to any of the excipients, or trace residues of tetracycline. Active or suspected malignancy. Patients with a history of malignancies in the gastrointestinal tract including the hepatobiliary system within the last five years.

Special warnings and precautions for use
Colo-rectal polyps
A colonoscopy with removal of polyps should be performed at the time of starting treatment. Yearly follow-up colonoscopies are recommended during the first 2 years. Subsequent colonoscopies are recommended at a minimum of five year intervals. An individual assessment whether increased frequency of surveillance is necessary should be performed based on the patient. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, therapy should be discontinued.

Gastrointestinal neoplasia including hepatobiliary tract
In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. These observations were not confirmed in clinical studies of more than one year duration. If a neoplasia is detected, it should be removed. In case of malignancy, treatment should be discontinued.

Gallbladder and bile ducts
Cases of cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, the need for continued treatment should be reassessed.

Pancreatic diseases
Chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies. In case of pancreatic adverse events, the need for continued treatment should be reassessed.

Monitoring of small bowel, gallbladder and bile ducts, and pancreas
SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This includes monitoring of short bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques.

Intestinal obstruction
Cases have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued treatment should be reassessed.

Cardiovascular
Patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during initiation of therapy. Patients should contact their physician in case of sudden weight gain, swollen ankles and/or dyspnoea. Fluid overload can be prevented by appropriate and timely assessment of parenteral nutrition needs. Assessment should be conducted more frequently within the first months of treatment. In case of a significant deterioration of the cardiovascular disease, the need for continued treatment should be reassessed.

Management of fluids during treatment
Parental support should be reduced carefully and should not be discontinued abruptly. The fluid status should be evaluated following parental support reduction and adjusted as needed.

Concomitant medication
Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption.

Special clinical conditions
Caution should be exercised when prescribing in patients with severe, clinically unstable concomitant diseases or with malignancies within the last five years.

Hepatic impairment
Revestive has not been studied in patients with severe hepatic impairment. The data from use in subjects with moderate hepatic impairment do not suggest a need for restricted use.

Discontinuation of treatment
Due to the risk of dehydration, discontinuation of treatment should be managed carefully.

Excipients
Revestive contains less than 1 mmol sodium (23 mg) per dose. This means that it is essentially 'sodium-free'. Caution is needed when administering Revestive to persons with a known hypersensitivity to tetracycline.

Colo-rectal polyps/Neoplasia (Paediatric population)
Prior to initiating treatment, faecal occult blood testing should be performed in all children. Subsequent testing should be conducted annually.
Children 12 years of age and older should undergo a colonoscopy / sigmoidoscopy prior to treatment initiation, unless one has been done within the past year. Children under 12 years of age should also have the procedure if they have unexplained blood in their stool. A colonoscopy is recommended for all children after one year of treatment, and at least every 5 years thereafter of continuous treatment is advised.

Adverse reactions

Very common (frequency ≥1/10)	Respiratory tract infection, headache, abdominal pain and distension, vomiting, nausea, gastrointestinal stoma complication*, oedema peripheral, injection site reaction.
Common (≥1/100 to <1/10)	Influenza, decreased appetite, anxiety, sleep disorder, paraesthesia, cardiac failure congestive, flushing, dyspnoea, cough, pancreatitis, intestinal obstruction, cholestasis and cholecystitis, dermatitis allergic, rash, arthalgia, renal colic, costovertebral angle tenderness, chest pain, night sweats, C-reactive protein increased.
Uncommon (≥1/1,000 to <1/100)	Syncope.

*Gastrointestinal stoma complication (swelling of the stoma and associated complications) is considered to be rather a sign of efficacy than an adverse reaction.

Please consult the Revestive Summary Product Characteristics (SmPC) before prescribing.

For EU Summary of Product Characteristics for Revestive in adults please click here. For the Revestive Product Monograph (Canada), please click here. For the U.S. Prescribing Information for Gattex, please click here.

For further information please contact:

Investor Relations		
Sarah Elton-Farr	seltonfarr@shire.com	+44 1256 894157
Ian Karp	ikarp@shire.com	+1 781 482 9018
Robert Coates	rcoates@shire.com	+44 1256 894874
Media		
Deborah Hibbett	dhibbett@shire.com	+41 41 288 4359
Clotilde Houze	chouze0@shire.com	+1 781 266 3567

NOTES TO EDITORS

About Shire

Shire is the leading global biotechnology company focused on serving people with rare diseases and other highly specialized conditions. We strive to develop best-in-class products, many of which are available in more than 100 countries, across core therapeutic areas including Hematology, Immunology, Neuroscience, Lysosomal Storage Disorders, Gastrointestinal / Internal Medicine / Endocrine and Hereditary Angioedema; a growing franchise in Oncology; and an emerging, innovative pipeline in Ophthalmics.

Our employees come to work every day with a shared mission: to develop and deliver breakthrough therapies for the hundreds of millions of people in the world affected by rare diseases and other high-need conditions, and who lack effective therapies to live their lives to the fullest.

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Forward-Looking Statements

Statements included herein that are not historical facts, including without limitation statements concerning future strategy, plans, objectives, expectations and intentions, the anticipated timing of clinical trials and approvals for, and the commercial potential of, inline or pipeline products are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, the following:

- disruption from the acquisition and integration of Baxalta Incorporated ("Baxalta") may make it more difficult to conduct business as usual or maintain relationships with patients, physicians, employees or suppliers;
- the company may not achieve some or all of the anticipated benefits of Baxalta's spin-off from Baxter International, Inc. ("Baxter") and the acquisition may have an adverse impact on

Baxalta's existing arrangements with Baxter, including those related to transition, manufacturing and supply services and tax matters;

- the failure to achieve the strategic objectives with respect to the acquisition of Baxalta may adversely affect the company's financial condition and results of operations;
- products and product candidates may not achieve commercial success;
- product sales from ADDERALL XR and INTUNIV are subject to generic competition;
- the failure to obtain and maintain reimbursement, or an adequate level of reimbursement, by third-party payers in a timely manner for the company's products may affect future revenues, financial condition and results of operations, particularly if there is pressure on pricing of products to treat rare diseases;
- supply chain or manufacturing disruptions may result in declines in revenue for affected products and commercial traction from competitors; regulatory actions associated with product approvals or changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, an increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- the successful development of products in various stages of research and development is highly uncertain and requires significant expenditures and time, and there is no guarantee that these products will receive regulatory approval;
- the actions of certain customers could affect the company's ability to sell or market products profitably, and fluctuations in buying or distribution patterns by such customers can adversely affect the company's revenues, financial condition or results of operations;
- investigations or enforcement action by regulatory authorities or law enforcement agencies relating to the company's activities in the highly regulated markets in which it operates may result in significant legal costs and the payment of substantial compensation or fines;
- adverse outcomes in legal matters, tax audits and other disputes, including the company's ability to enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on the company's revenues, financial condition or results of operations;
- Shire is undergoing a corporate reorganization and was the subject of an unsuccessful acquisition proposal and the consequent uncertainty could adversely affect the company's ability to attract and/or retain the highly skilled personnel needed to meet its strategic objectives;
- failure to achieve the strategic objectives with respect to Shire's acquisition of NPS Pharmaceuticals Inc. or Dyax Corp. ("Dyax") may adversely affect the company's financial condition and results of operations;
- the company is dependent on information technology and its systems and infrastructure face certain risks, including from service disruptions, the loss of sensitive or confidential information, cyber-attacks and other security breaches or data leakages that could have a material adverse effect on the company's revenues, financial condition or results of operations;
- the company may be unable to retain and hire key personnel and/or maintain its relationships with customers, suppliers and other business partners;
- difficulties in integrating Dyax or Baxalta into Shire may lead to the company not being able to realize the expected operating efficiencies, cost savings, revenue enhancements, synergies or other benefits at the time anticipated or at all; and
- other risks and uncertainties detailed from time to time in Shire's, Dyax's or Baxalta's filings with the Securities and Exchange Commission, including those risks outlined in "ITEM 1A: Risk Factors" in Shire's and Baxalta's Annual Reports on Form 10-K for the year ended December 31, 2015.

All forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by this cautionary statement. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. Except to the extent otherwise required by applicable law, we do not undertake any obligation to republish revised forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events.

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