

Intended for global audience

Health Canada has authorized TAKHZYRO™ (lanadelumab injection), a first-of-its-kind monoclonal antibody treatment for the prevention of hereditary angioedema (HAE) attacks

New treatment option for HAE receives first international marketing authorization outside of the U.S.

Cambridge, MA – September 20, 2018 – Shire plc (LSE: SHP, NASDAQ: SHPG) and Shire Pharma Canada ULC (Shire Canada), the leading global biotechnology company focused on rare diseases, announced today that following priority review, Health Canada has authorized TAKHZYRO (lanadelumab injection) for routine prevention of attacks of hereditary angioedema (HAE) in adolescents and adults (12 years of age and older). HAE is a rare, genetic and potentially life-threatening disorder that can result in recurrent attacks of edema (swelling) in various parts of the body. HAE attacks can happen spontaneously at any time and can be debilitating and painful.

"The burden HAE patients and their families face every day can't be ignored," said Jacquie Badiou, President, HAE Canada. "Our National Report Card shows that the unpredictable nature of this life-threatening disorder, not knowing when the next attack will come, has a negative impact on their lives and the lives of their loved ones. This new treatment option is great news as it was shown to significantly reduce the frequency of attacks."

TAKHZYRO is a fully human monoclonal antibody that inhibits the activity of plasma kallikrein, an enzyme which is uncontrolled in people with HAE, to prevent attacks. The recommended dose of TAKHZYRO is 300 mg every 2 weeks. A dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.

Health Canada's authorization of TAKHZYRO for the routine prevention of HAE attacks in adolescents and adults is supported by results of the Phase III HELP (Hereditary Angioedema Long-term Prophylaxis) Study, in which the primary efficacy endpoint was the number of investigator-confirmed HAE attacks during the 26-week study duration. The HELP study demonstrated that TAKHZYRO reduced the number of monthly HAE attacks by an average of 87 per cent (n=27) vs. placebo (n=41) when administered at 300 mg every two weeks and 73 per cent (n=29) vs. placebo (n=41) when administered at 300 mg every four weeks ($P<0.001$).

In the 26-week clinical study, which enrolled 125 patients with HAE with C1 inhibitor deficiency, secondary endpoints included: the number of attacks requiring acute treatment and the number of attacks assessed as moderate or severe. Patients taking TAKHZYRO 300 mg every two weeks had 87 per cent fewer attacks that required on-demand treatment and 83 per cent fewer moderate to severe attacks. A pre-specified, exploratory analysis showed that 44 per cent of patients (n=27) receiving TAKHZYRO 300 mg every two weeks had zero attacks compared to placebo (2 per cent, n=41) for the 26-week treatment period.

Of the patients who received TAKHZYRO and completed the HELP Study, the largest prevention study conducted to date in HAE, 97 per cent enrolled in an ongoing open-label extension study designed to evaluate the long-term safety and efficacy of TAKHZYRO. In the extension study, after receiving a single dose of TAKHZYRO 300 mg at study entry, 80 per cent of patients who had been in the 300 mg every two weeks treatment group (n=25) in the HELP Study remained attack-free at week 4 post-dose.

The most common side effects seen with TAKHZYRO were injection site reactions including pain, redness, and bruising.

“As a physician who treats patients with HAE, I am pleased to have a treatment like TAKHZYRO available for the prevention of HAE attacks,” said Dr. Stephen D Betschel. “The HAE community has a new option that can help prevent attacks.”

TAKHZYRO has a half-life of approximately 14 days and can be self-administered every two or four weeks as one subcutaneous injection. In the HELP Study extension the majority of self-injections took one minute or less to complete.

“This authorization reinforces our ongoing commitment to develop innovative therapies that can help make a positive impact on patients,” said Eric Tse, General Manager, Shire Canada. “We will continue to work towards our goal of improving the lives of those living with rare diseases, including HAE.”

TAKHZYRO was approved in the U.S. on August 23, 2018 for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years of age and older. Additional regulatory submissions are ongoing worldwide.

About The HELP Study

The HELP Study was a global, multicentre, randomized, double-blind placebo-controlled parallel group trial that evaluated the efficacy and safety of subcutaneously administered TAKHZYRO vs. placebo over 26 weeks in 125 patients 12 years of age or older with HAE.

The primary endpoint was the number of investigator-confirmed HAE attacks over the entire 26-week study duration. TAKHZYRO demonstrated that subcutaneous injections every two or four weeks reduced the mean monthly number of attacks across all three TAKHZYRO treatment arms studied: 300 mg every two weeks, 300 mg every four weeks, and 150 mg of TAKHZYRO every four weeks. At 300 mg every two weeks, TAKHZYRO reduced the number of mean monthly HAE attacks by 87 per cent vs. placebo ($P<0.001$).

Secondary endpoints included: 1) number of attacks requiring acute treatment, 2) number of attacks assessed as moderate or severe and 3) number of attacks from days 14-182. Overall, each TAKHZYRO treatment arm demonstrated statistically significant attack rate reductions compared with placebo for all secondary efficacy endpoints (adjusted $P<0.001$ for all comparisons), including: attacks requiring acute treatment (74 per cent to 87 per cent) and moderate or severe attacks (70 per cent to 83 per cent).

The HELP Study Extension

The long-term safety and efficacy of TAKHZYRO for the prevention of HAE attacks continues to be evaluated in an open-label extension study.

In the extension study, 212 adolescent and adult patients received at least one dose of TAKHZYRO. Of these, 109 patients are rollover participants from the HELP Study and 103 are new (non-rollover) participants who had a historical baseline attack rate of ≥ 1 attack per 12 weeks and a confirmed diagnosis of HAE.

About Hereditary Angioedema

HAE is a rare, genetic disorder estimated to affect about 1 in 10,000 to 1 in 50,000 people worldwide. Around 900 HAE patients are estimated to be in Canada. The condition results in recurring attacks of edema (swelling) in various parts of the body that can be debilitating and painful. Laryngeal attacks that obstruct the airways are potentially life-threatening due to the risk of asphyxiation. Aside from the burden of the disease itself, patients can suffer anxiety, fatigue and depression between attacks.

About TAKHZYRO (lanadelumab injection)

TAKHZYRO (lanadelumab injection) is indicated for routine prevention of attacks of hereditary angioedema (HAE) in adolescents and adults (12 years of age and older).

TAKHZYRO is not intended for acute treatment of HAE attacks. Patients and caregivers should continue to be prepared to treat attacks with acute HAE treatments when necessary.

TAKHZYRO is a fully human monoclonal antibody that specifically binds and inhibits plasma kallikrein activity and is indicated for the prevention of HAE attacks in patients 12 years and older. TAKHZYRO is formulated for subcutaneous administration and has a half-life of approximately two weeks in patients with HAE. TAKHZYRO is intended for self-administration or administration by a caregiver. The patient or caregiver should be trained by a healthcare professional.

It is not known if TAKHZYRO is safe and effective in children under 12 years of age.

IMPORTANT SAFETY INFORMATION FROM THE CANADIAN PRODUCT MONOGRAPH**Hypersensitivity**

Hypersensitivity reactions have been observed with TAKHZYRO. In case of a severe hypersensitivity reaction, discontinue TAKHZYRO (lanadelumab injection) administration and institute appropriate treatment.

Adverse Reactions

In clinical trials, the most commonly observed adverse reactions associated with TAKHZYRO in subjects with HAE were injection site reactions (ISR) including injection site pain, injection site erythema and injection site bruising. Most were of mild intensity and resolved within 1 day after onset. Other common adverse reactions (>1 per cent) included hypersensitivity, myalgia (muscle pain), dizziness, elevated levels of transaminases, and raised skin rash/skin redness.

Use in Specific Populations

The safety and efficacy of TAKHZYRO in pediatric patients < 12 years of age have not been studied.

TAKHZYRO has not been studied in pregnant or lactating women. It is unknown if TAKHZYRO is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

To report SUSPECTED ADVERSE REACTIONS, contact Shire at drugsafety@shire.com, or Health Canada at 1-866-234-2345 or <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>

Please see full Prescribing Information within the [Canadian Product Monograph](#).

Shire's Commitment to Hereditary Angioedema

Shire is a dedicated, long-term partner to the HAE community with a decade of experience supporting patients. We are committed to serial innovation in HAE and our portfolio of products includes a number of therapy options to help meet the individual needs of those living with the disease. Beyond our focus on developing novel treatments, we provide specialized services and support offerings tailored to the HAE community. Learn more at www.shire.com.

TAKHZYRO is a trademark or registered trademark of Dyax Corp., a Shire plc affiliate. SHIRE and the Shire Logo are trademarks or registered trademarks of Shire Pharmaceuticals Ireland Limited, a Shire plc affiliate.

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NOTE TO EDITORS

About Shire

Shire is the global biotechnology leader serving patients with rare diseases and specialized conditions. We seek to push boundaries through discovering and delivering new possibilities for patient communities who often have few or no other champions. Relentlessly on the edge of what's next, we are serial innovators with a diverse pipeline offering fresh thinking and new hope. Serving patients and partnering with healthcare communities in over 100 countries, we strive to be part of the entire patient journey to enable earlier diagnosis, raise standards of care, accelerate access to treatment, and support patients. Our diverse portfolio of therapeutic areas includes Immunology, Hematology, Genetic Diseases, Neuroscience, Internal Medicine and Ophthalmics.

Championing patients is our call to action - it brings the opportunity - and responsibility - to change people's lives.

www.shire.com

About Shire Pharma Canada ULC

Shire Pharma Canada ULC is a subsidiary of Shire. Our Canadian office is located in Toronto, Ontario. For more information, please visit: www.shirecanada.com.

Forward-Looking Statements

Statements included herein that are not historical facts, including without limitation statements concerning future strategy, plans, objectives, expectations and intentions, projected revenues, 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:

- Shire's products may not be a commercial success;
- increased pricing pressures and limits on patient access as a result of governmental regulations and market developments may affect Shire's future revenues, financial condition and results of operations;
- Shire depends on third parties to supply certain inputs and services critical to its operations including certain inputs, services and ingredients critical to its manufacturing processes. Any disruption to the supply chain for any of Shire's products may result in Shire being unable to continue marketing or developing a product or may result in Shire being unable to do so on a commercially viable basis for some period of time;
- the manufacture of Shire's products is subject to extensive oversight by various regulatory agencies. Regulatory approvals or interventions associated with changes to

manufacturing sites, ingredients or manufacturing processes could lead to, among other things, significant delays, an increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;

- the nature of producing plasma-based therapies may prevent Shire from timely responding to market forces and effectively managing its production capacity;
- Shire has a portfolio of products in various stages of research and development. The successful development of these products 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 Shire's ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such customers can adversely affect Shire's revenues, financial conditions or results of operations;
- failure to comply with laws and regulations governing the sales and marketing of its products could materially impact Shire's revenues and profitability;
- Shire's products and product candidates face substantial competition in the product markets in which it operates, including competition from generics;
- Shire's patented products are subject to significant competition from generics;
- adverse outcomes in legal matters, tax audits and other disputes, including Shire's ability to enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on Shire's revenues, financial condition or results of operations;
- Shire may fail to obtain, maintain, enforce or defend the intellectual property rights required to conduct its business;
- Shire faces intense competition for highly qualified personnel from other companies and organizations;
- failure to successfully execute or attain strategic objectives from Shire's acquisitions and growth strategy may adversely affect Shire's financial condition and results of operations;
- Shire's growth strategy depends in part upon its ability to expand its product portfolio through external collaborations, which, if unsuccessful, may adversely affect the development and sale of its products;
- a slowdown of global economic growth, or economic instability of countries in which Shire does business, could have negative consequences for Shire's business and increase the risk of non-payment by Shire's customers;
- changes in foreign currency exchange rates and interest rates could have a material adverse effect on Shire's operating results and liquidity;
- Shire is subject to evolving and complex tax laws, which may result in additional liabilities that may adversely affect Shire's financial condition or results of operations;
- if a marketed product fails to work effectively or causes adverse side effects, this could result in damage to Shire's reputation, the withdrawal of the product and legal action against Shire;
- Shire 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 Shire's revenues, financial condition or results of operations;
- Shire faces risks relating to the expected exit of the United Kingdom from the European Union;
- Shire incurred substantial additional indebtedness to finance the Baxalta acquisition, which has increased its borrowing costs and may decrease its business flexibility;
- the potential uncertainty among our employees, customers, suppliers, and other business partners resulting from the announcement by Takeda Pharmaceutical Company Limited on May 8, 2018 of a recommended offer for Shire under the UK Takeover Code; and

a further list and description of risks, uncertainties and other matters can be found in Shire's most recent Annual Report on Form 10-K and in Shire's subsequent Quarterly Reports on Form 10-Q, in each case including those risks outlined in "ITEM1A: Risk Factors", and in Shire's

subsequent reports on Form 8-K and other Securities and Exchange Commission filings, all of which are available on Shire's website.

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 update or revise forward-looking statements, whether as a result of new information, future events or otherwise.