

Shire Announces FDA Approval of Once-Daily INTUNIV™ (guanfacine) Extended Release Tablets for the Treatment of ADHD in Children and Adolescents Aged 6 to 17

INTUNIV, the first nonscheduled alpha-2A receptor agonist indicated for ADHD, demonstrated improvement in a range of ADHD symptoms that can be disruptive, such as inattention, arguing with adults, hyperactivity, impulsivity, and losing one's temper.

September 03, 2009 – [Shire plc](#) (LSE: SHP, NASDAQ: SHPGY), the global specialty biopharmaceutical company, today announced that it has received approval from the US Food and Drug Administration (FDA) for [INTUNIV™](#) (guanfacine) Extended Release Tablets for the treatment of Attention-Deficit/Hyperactivity Disorder ([ADHD](#)) in children and adolescents aged 6 to 17 years. INTUNIV, a once-daily formulation of guanfacine, is the first selective alpha-2A adrenergic receptor agonist approved for the treatment of ADHD. Although the mechanism of action is unknown, INTUNIV is thought to directly engage receptors found in the prefrontal cortex – an area of the brain that has been linked in preclinical research to ADHD. Stimulation of the postsynaptic alpha-2A receptors is thought to strengthen working memory, reduce susceptibility to distraction, improve attention regulation, improve behavioral inhibition, and enhance impulse control.

“Shire is proud to introduce [INTUNIV](#), providing clinicians, patients, and their families with a novel ADHD treatment option,” said Mike Cola, President of Shire Specialty Pharmaceuticals. “This is a complex disorder in which patients may present with multiple symptoms and behaviors that can be disruptive. INTUNIV expands the Shire ADHD portfolio with a nonscheduled medication, allowing clinicians to optimize their overall approach toward managing ADHD and may help provide symptom control for children and teens with ADHD who often have difficulty responding appropriately to everyday situations and challenges.”

Once-daily [INTUNIV](#) is expected to be available in US pharmacies in November and will come in four dosage strengths (1 mg, 2 mg, 3 mg, and 4 mg). INTUNIV will be marketed in the United States by the existing Shire ADHD sales team of nearly 600 representatives. INTUNIV is not a controlled substance and has no known potential for abuse or dependence.

“Everyday situations and challenges may be difficult for children and adolescents with ADHD as it is a disruptive disorder that includes symptoms and behaviors such as being easily distracted, always on the go, interrupting others, arguing with adults, or temper outbursts,” said Frank A. López, MD, a neurodevelopmental pediatrician in private practice at Children’s Developmental Center in Winter Park, Florida. “In clinical trials, INTUNIV, a selective alpha-2A receptor agonist, significantly reduced [ADHD symptoms](#) across a full day as measured by parents at 6 PM, 8 PM, and 6 AM the next morning. This is important because children with ADHD require symptom control at home, school, and during after school activities.”

The introduction of INTUNIV is consistent with the strategy of Shire to expand and diversify its ADHD portfolio, which now consists of four [ADHD treatment](#) options of scheduled and nonscheduled medicines in the United States and two ADHD medicines available outside the United States.

Additional information about INTUNIV and Full Prescribing Information are available at <http://www.intuniv.com>.

INTUNIV Demonstrated Significant Reduction in ADHD Symptoms

The efficacy of INTUNIV in the treatment of ADHD was established in two, similarly designed, placebo-controlled clinical trials in children and adolescents aged 6 to 17 years who met *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV®)* criteria for ADHD. Statistically significant improvements were reported by investigators, parents, and teachers.

The first pivotal trial was a phase III, double-blind, parallel-group trial, in which investigators randomized 345 children aged 6 to 17 years to either a placebo or a fixed 2-mg, 3-mg, or 4-mg dose of INTUNIV given once daily during an eight-week period. The second pivotal trial was a phase III, double-blind, parallel-group trial, in which investigators randomized 324 children aged 6 to 17 years to either a placebo or a fixed 1-mg, 2-mg, 3-mg, or 4-mg dose of INTUNIV given once daily during a nine-week period, with the 1 mg assigned only to patients weighing less than 50 kg (110 lbs).

In both trials, doses were increased in increments of 1 mg per week, and investigators evaluated participants' signs and symptoms of ADHD on a once-weekly basis using the clinician administered and scored ADHD Rating Scale-IV (ADHD-RS-IV), a scale frequently used in ADHD clinical trials that assesses hyperactive, impulsive, and inattentive symptoms. The primary outcome was the change in total ADHD-RS-IV scores from baseline to end point in both studies.

Both trials demonstrated statistically significant improvements in ADHD-RS-IV scores in patients taking INTUNIV beginning one to two weeks after patients began receiving once-daily doses of INTUNIV. In the first pivotal trial, the mean reduction in ADHD-RS-IV total scores at end point were -16.7 for INTUNIV compared to -8.9 for placebo ($P<.0001$), the mean reduction in ADHD-RS-IV total scores in the second pivotal trial were -19.6 for INTUNIV and -12.2 for placebo ($P=.0040$). Placebo-adjusted LS mean changes from baseline were statistically significant for all INTUNIV doses in the randomized treatment groups in both studies.

Additional secondary efficacy outcome measures included the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R). CPRS-R and CTRS-R are comprehensive scales that use parent and teacher observer and self-report ratings to help assess ADHD and evaluate behavioral issues in children and adolescents. Among some of the symptoms measured were: inattentiveness/being easily distracted, running around or climbing excessively, arguing with adults, losing temper, and interrupting or intruding on others. Significant improvements were seen on both scales: based on the CPRS-R, parents reported significant improvement across a full day (as measured at 6 PM, 8 PM, and 6 AM the next morning); based on the CTRS-R, which was used only in the first pivotal trial, teachers reported significant improvement throughout the school day (as measured at 10 AM and 2 PM).

Investigators also measured the efficacy of INTUNIV with the Clinical Global Impressions-Improvement (CGI-I) scale, a standard assessment used to rate the improvement of a patient's illness over the course of the study. The first pivotal trial found the percentage of subjects taking INTUNIV who were rated "much improved" or "very much improved" at end point ranged from approximately 50 to 56 percent across all doses versus approximately 26 percent for placebo ($P<.05$). Subjects taking INTUNIV in the second pivotal trial who rated "much improved" or "very much improved" at end point ranged from 54 to 56 percent across 1-mg ($P=.0070$), 3-mg ($P=.0060$), and 4-mg ($P=.0040$) doses versus 30 percent for placebo; the placebo-INTUNIV difference for the 2-mg dose was not significant ($P=.1404$).

Safety was also evaluated during these pivotal trials and safety data showed that adverse events reported by participants using INTUNIV were generally mild to moderate in severity, with the most common side effects being sedative in nature. Sedation-related, treatment-emergent adverse events were among the most common and were usually transient and mild to moderate in severity. Treatment-related adverse events greater than 10 percent included somnolence (32 percent), headache (26 percent), fatigue (18 percent), upper abdominal pain (14 percent), and sedation (13 percent). Small to modest changes in blood pressure, pulse rate, and ECG parameters were observed.

Important Safety Information

INTUNIV is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents aged 6 to 17. Efficacy was established in two controlled clinical trials (8 and 9 weeks in duration). The physician electing to use INTUNIV for extended periods should periodically reevaluate its long-term usefulness for the individual patient.

INTUNIV should not be used in patients with a history of hypersensitivity to guanfacine or any of its inactive ingredients or by patients taking other products containing guanfacine

Hypotension, bradycardia, and syncope were observed in clinical trials. Use INTUNIV with caution in treating patients who have experienced hypotension, bradycardia, heart block, or syncope, or who may have a condition that predisposes them to syncope; are treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Heart rate and blood pressure should be measured prior to initiation of therapy, following dose increases, and periodically while on therapy. Patients should be advised to avoid becoming dehydrated or overheated.

Sedation and somnolence were commonly observed in clinical trials. The potential for additive sedative effects with CNS depressant drugs should be considered. Patients should be cautioned against operating heavy equipment or driving until they know how they respond to INTUNIV.

Common adverse reactions in patients taking INTUNIV that may be dose-related over the range of 1 to 4 mg/day include somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth, and constipation.

About ADHD

ADHD is one of the most common psychiatric disorders in children and adolescents. Worldwide prevalence of ADHD is estimated at 5.3 percent (with large variability), according to a comprehensive systematic review of this topic published in 2007 in the *American Journal of Psychiatry*. In the United States, approximately 7.8 percent of all school-aged children, or about 4.4 million children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the Centers for Disease Control and Prevention (CDC). The disorder is also estimated to affect 4.4 percent of US adults aged 18 to 44 based on results from the National Comorbidity Survey Replication. When this percentage is extrapolated to the full US population aged 18 and over, approximately 9.8 million adults are believed to have ADHD.

ADHD is a psychiatric behavioral disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. The specific etiology of ADHD is unknown and there is no single diagnostic test for this syndrome. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources, utilizing diagnostic criteria such as *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV®)* or *International Classification of Diseases 10 (ICD-10)*.

Although there is no cure for ADHD, there are accepted treatments that specifically target its symptoms. Standard treatments include educational approaches, psychological or behavioral modification, and medication.

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Notes to editors

SHIRE PLC

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit hyperactivity disorder (ADHD), human genetic therapies (HGT) and gastrointestinal (GI) diseases as well as opportunities in other therapeutic areas to the extent they arise through acquisitions. Shire's in-licensing, merger and acquisition efforts are focused on products in specialist markets with strong intellectual property protection and global rights. Shire believes that a carefully selected and balanced portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

For further information on Shire, please visit the Company's website: www.shire.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts 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, the Company's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of research, development, approval, reimbursement, manufacturing and commercialization of the Company's Specialty Pharmaceutical and Human Genetic Therapies products, as well as the ability to secure and integrate new products for commercialization and/or development; government regulation of the Company's products; the Company's ability to manufacture its products in sufficient quantities to meet demand; the impact of competitive therapies on the Company's products; the Company's ability to register, maintain and enforce patents and other intellectual property rights relating to its products; the Company's ability to obtain and maintain government and other third-party reimbursement for its products; and other risks and uncertainties detailed from time to time in the Company's filings with the Securities and Exchange Commission.

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