FDA Approves Supplemental New Drug Application for Myrbetriq® (mirabegron) for Use in Combination with solifenacin succinate for the Treatment of Overactive Bladder Symptoms

TOKYO, May 7, 2018 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") announced today that the U.S. Food and Drug Administration (FDA) has approved a supplemental New Drug Application (sNDA) for the use of mirabegron in combination with the muscarinic antagonist solifenacin succinate for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency.[1]

In the United States, mirabegron and solifenacin succinate are marketed as Myrbetriq® and VESIcare®, respectively. Each is approved by the FDA as a monotherapy for OAB.[1, 2]

"OAB patients may have symptoms that are not fully managed with their current treatment," said Carol Schermer, M.D., M.P.H., senior medical director, urology, Astellas. "With the FDA approval of Myrbetriq in combination with solifenacin succinate, Astellas is able to offer an additional treatment option to individuals living with symptoms of OAB."

The sNDA submission was based on data from the global Phase 3 SYNERGY I, SYNERGY II and BESIDE studies. These studies evaluated combination therapy with mirabegron and solifenacin succinate compared with each drug as monotherapy or placebo.[3, 4, 5]

About the SYNERGY I Trial
The Phase 3 SYNERGY I trial enrolled 6,991 patients across 435 study locations in 42 countries.[3] The trial evaluated the safety profile of combinations of mirabegron and solifenacin succinate compared with each drug as monotherapy and placebo in patients who had experienced symptoms of "wet" OAB (urinary frequency and urgency with incontinence) for at least 3 months.

About the SYNERGY II Trial
The 52-week, Phase 3 SYNERGY II trial enrolled 2,084 patients across 251 sites in 32 countries.[4] The trial evaluated the long term safety profile of combination of mirabegron 50 mg and solifenacin succinate 5 mg compared with each drug as monotherapy in patients who had experienced symptoms of "wet" OAB (urinary frequency and urgency with incontinence) for at least 3 months.

About the BESIDE Trial
The Phase 3b BESIDE study enrolled 2,174 patients across 281 sites in 31 countries.[5] The trial evaluated the efficacy, safety and tolerability of mirabegron 50 mg as an add-on therapy with solifenacin succinate 5 mg versus solifenacin

succinate 5 mg and 10mg alone in OAB patients who had inadequate response to treatment with solifenacin succinate monotherapy.

About Overactive Bladder (OAB)
Overactive bladder is a urine storage problem of urgency, with or without urge urinary incontinence (leakage), often with urinary frequency and nocturia.[6] It has been estimated by this year, 546 million people worldwide will be affected by OAB.[7] For people with OAB, inappropriate signals are sent to the muscles in the bladder causing them to contract before the bladder is full.[8] These bladder contractions may cause strong, sudden urges, and a frequent need to go to the bathroom.

Indications and Usage
Myrbetriq® (mirabegron), a beta-3 adrenergic agonist, is indicated as monotherapy or in combination with the muscarinic antagonist solifenacin succinate for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Important Safety Information
Do not use Myrbetriq in patients who have known hypersensitivity reactions to mirabegron or any component of the tablet.

Solifenacin succinate is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients with hypersensitivity to the product.

Myrbetriq alone or in combination with solifenacin succinate can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Myrbetriq is not recommended for use in severe uncontrolled hypertensive patients (defined as systolic blood pressure ≥ 180mm Hg and/or diastolic blood pressure ≥ 110mm Hg). Worsening of hypertension was reported infrequently in Myrbetriq clinical trial patients with OAB.

In patients taking Myrbetriq, urinary retention has been reported in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Myrbetriq patients; however, Myrbetriq and solifenacin succinate should still be administered with caution to patients with clinically significant BOO. For example, monitor these patients for signs and symptoms of urinary retention. Myrbetriq should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB, including solifenacin succinate.

Angioedema of the face, lips, tongue and/or larynx has been reported with Myrbetriq and with solifenacin succinate. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue Myrbetriq and/or solifenacin succinate and initiate appropriate therapy and/or measures necessary to ensure a patent airway.

Solifenacin succinate should be administered with caution to patients with decreased gastrointestinal motility, controlled narrow-angle glaucoma or reduced renal or hepatic function. Doses of solifenacin succinate higher than 5mg are not recommended in patients with severe renal impairment, moderate hepatic impairment, or when administered with ketoconazole or other potent CYP3A4 inhibitors. Use of solifenacin succinate in patients with severe hepatic impairment is not recommended.

Anticholinergic central nervous system (CNS) effects have been reported with solifenacin succinate use, including headache, confusion, hallucinations and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing dose, and be advised not to drive or operate heavy machinery until they know how solifenacin succinate affects them. If a patient experiences these effects, dose reduction or drug discontinuation should be considered.

Since Myrbetriq is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with Myrbetriq. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone.

In solifenacin succinate monotherapy studies, for the 5mg dose one serious adverse event (angioneurotic edema) was reported. For the 10mg dose, three intestinal serious adverse events were reported (one fecal impaction, one colonic obstruction and one intestinal obstruction).

In clinical trials, the most commonly reported adverse reactions (> 2% and > placebo) for Myrbetriq 25mg and 50mg versus placebo, respectively, were hypertension (11.3%, 7.5% vs. 7.6%), nasopharyngitis (3.5%, 3.9% vs. 2.5%), urinary tract infection (4.2%, 2.9% vs. 1.8%), and headache (2.1%, 3.2% vs. 3.0%).

In clinical trials, the most commonly reported adverse reactions (> 2% and > placebo and > comparator) for Myrbetriq in combination with solifenacin succinate 25mg + 5mg and 50mg + 5mg versus Myrbetriq 25mg, Myrbetriq 50mg, solifenacin succinate 5mg and placebo, respectively, were dry mouth (9.3%, 7.2% vs. 3.8%, 3.6%, 6.5%, 2.2%), urinary tract infection (7.0%, 4.0% vs. 4.0%, 4.2%, 3.6%, 5.3%), constipation (4.2%, 3.9% vs. 1.2%, 2.8%, 2.4%, 1.2%), and tachycardia (2.2%, 0.9% vs. 1.6%, 1.6%, 0.7%, 0.8%).

In postmarketing experience with mirabegron, the following events have also occurred: atrial fibrillation, nausea, constipation, diarrhea, and dizziness.

Please see accompanying complete Prescribing Information for Myrbetriq® (mirabegron) and VESIcare® (solifenacin succinate).

About Astellas
Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. We focus on Urology, Oncology, Immunology, Nephrology and Neuroscience as prioritized therapeutic areas while advancing new therapeutic areas and discovery research leveraging new technologies/modalities. We are also creating new value by combining internal capabilities and external expertise in the medical/healthcare business. Astellas is on the forefront of healthcare change to turn innovative science into value for patients. For more information, please visit our website at https://www.astellas.com/en.

Cautionary Notes
In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

References:

1. Myrbetriq [package insert]. Northbrook, IL; Astellas, Inc.
2. VESIcare [package insert]. Northbrook, IL: Astellas, Inc.
3. Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int 2017;120(4):562-75.
4. ClinicalTrials.gov. A Randomized, Double-Blind, Parallel-Group, Active-Controlled, Multi-center Study to Evaluate the Long-Term Safety and Efficacy of Combination of Solifenacin Succinate With Mirabegron Compared to Solifenacin Succinate and Mirabegron Monotherapy in Subjects With Overactive Bladder (09-21-2017). https://clinicaltrials.gov/ct2/show/study/NCT02045862. Accessed 02-22-2018.
5. Drake MJ, Chapple C, Esen AA, et al. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised double-blind multicentre phase 3B study (BESIDE). Eur Urol 2016;70(1):136-45.
6. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61(1):37-49.
7. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011;108(7):1132-8.
8. Sadananda P, Drake MJ, Paton JFR, Pickering AE. A functional analysis of the influence of β3-adrenoceptors on the rat micturition cycle. J Pharmacol Exp Ther 2013;347(2):506-15.

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Contacts for inquiries or additional information:

Astellas Pharma Inc.
Corporate Communications:
Candace Johnson, candace.johnson@astellas.com
+1-224-205-5735
Investor Relations:
Shin Okubo, shin.okubo@astellas.com
+81-3-3244-3202