# News Release

**Takeda Receives Simultaneous European Marketing Authorization for Three New Type 2 Diabetes Therapies, *Vipidia*™ (alogliptin) and Fixed-Dose Combinations *Vipdomet*™ (alogliptin and metformin) and *Incresync*™ (alogliptin and pioglitazone)**

**Osaka, Japan, September 24, 2013** – Takeda Pharmaceutical Company Limited (Takeda) today announced that the European Commission has granted Marketing Authorization (MA) for *Vipidia*™ (alogliptin), a dipeptidyl peptidase IV (DPP-4) inhibitor, for the treatment of type 2 diabetes patients who are uncontrolled on existing therapies[1-3]and for the fixed-dose combination (FDC) therapies *Vipdomet*™ (alogliptin with metformin) and *Incresync*™ (alogliptin with pioglitazone). The Committee for Medicinal Products for Human Use (CHMP), of the European Medicines Agency (EMA), issued a positive opinion for these products on July 26, 2013.

This announcement, comes shortly after publication of final results from the cardiovascular (CV) safety outcomes trial EXAMINE* in *The New England Journal of Medicine (NEJM)*.[1] Alogliptin is the first agent for the treatment of type 2 diabetes to be licensed with demonstrated CV safety outcomes data.[4]

*"The incidence of type 2 diabetes in Europe is on the rise with an estimated 55 million cases in 2011 predicted to increase to an estimated 64.2 million in 2030"* said Trevor Smith, Head of Commercial Operations, Europe & Canada, Takeda. *"We know that many people living with type 2 diabetes struggle to manage their disease so there is a need for new therapies to assist them in doing so. This Marketing Authorization marks an important milestone in Takeda's ongoing commitment in working to advance patient care and helping to meet the individual needs of this growing patient population."*

The MA was based on data from a robust clinical trial program involving more than 11,000 patients treated for up to four years and two key studies the ENDURE† trial and interim data from the cardiovascular safety outcomes trial EXAMINE.

Results from the ENDURE study demonstrated that alogliptin 25 mg in addition to metformin offered superior durability of glycemic control at two years with notably fewer hypoglycemic episodes and no negative impact on weight compared to a sulphonylurea (SU), (glipizide).[5] Results also showed that when alogliptin was given in combination with metformin, significantly more patients achieve target $HbA_{1c}$ of ≤ 7% compared with an SU in combination with metformin.[5]

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* **EX**amination of C**A**rdiovascular Outco**M**es: Alogliptin vs. Standard of Car**E** in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome

† Efficacy and Safety of Alogliptin Plus Metformin Compared to Glipizide Plus Metformin in Subjects With Type 2 Diabetes Mellitus;

The efficacy of alogliptin was also studied as an adjunct to diet and exercise as an add-on therapy to several other classes of anti-diabetic medications, including metformin, thiazolidinediones (TZDs), insulin and SUs. In these studies alogliptin 25 mg tablets taken once daily, demonstrated clinically and statistically significant reductions in $HbA_{1c}$, with a good overall tolerability profile and low incidence of hypoglycemia compared with active control or placebo.[1, 6-10] Previous trials indicated that alogliptin co-administered with either metformin or pioglitazone produced significant improvements in glycemic control compared with the respective monotherapies.[11-13]

Common adverse events reported with alogliptin include upper respiratory tract infection, nasopharyngitis, headache, abdominal pain, gastroeosophageal reflux (GERD), pruritus and rash.[1] In patients treated with alogliptin co-administered with metformin, common adverse events include upper respiratory tract infection, nasopharyngitis, headache, abdominal pain, GERD, diarrhea, vomiting, gastritis, gastroenteritis, pruritus and rash.[2] Common adverse events reported with patients treated with alogliptin co-administered with pioglitazone include upper respiratory tract infection, sinusitis, nausea, dyspepsia, abdominal pain, pruritus, peripheral edema and increased weight.[3]

*"Although there are a number of treatment options already available, many patients still fail to meet glycemic targets, experience hypoglycemic episodes, are overweight and remain at risk from long-term complications, such as cardiovascular disease and renal impairment,"* commented Professor Simon Heller, Professor of Clinical Diabetes at the University of Sheffield, Sheffield, UK and EXAMINE trial investigator. "*Today's announcement, along with the cardiovascular outcomes data from EXAMINE, means that physicians within the European Union will have access to a comprehensive range of new treatments to help eligible patients manage their disease. Flexible treatments that are convenient for patients and that can help to control the numerous and complex factors associated with type 2 diabetes, may be of value in helping to implement a more personalized approach to care."*

Alogliptin is available in a range of doses suitable to treat patients with all stages of renal impairment, including end stage renal disease (ESRD).[1]

Takeda received approval for alogliptin (*Nesina*) in 2010 and in fixed-dose combination with pioglitazone (*Liovel*) in 2011 in Japan. In the US, Takeda received approval for alogliptin as a monotherapy (*Nesina)* and in fixed-dose combinations with metformin (*Kazano*) and with pioglitazone (*Oseni*) in 2013. In addition, alogliptin was approved in China in 2013.

The approval of these MAs will not require any change of the outlook for Takeda's consolidated results for the full year of fiscal 2013 announced on July 31, 2013.

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**About *Vipidia* (alogliptin)**

- Alogliptin is indicated for the treatment of type 2 diabetes in adults aged 18 years and older to improve glycemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycemic control[1]
- The usual recommended daily dose is 25 mg once daily (OD), with dose flexibility for all stages of renal impairment (no dose adjustment for mild renal impairment, 12.5 mg OD for moderate renal impairment, 6.25 mg OD for severe renal impairment or ESRD)[1]
- DPP-4 inhibitors address insulin deficiency by slowing the inactivation of incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide).[14] As a result, an increased amount of active incretins enables the pancreas to secrete insulin in a glucose-dependent manner, thereby assisting in the management of blood glucose levels[14]

Alogliptin is currently available in Japan and the US under the brand name *Nesina*.

**About *Vipdomet* (alogliptin and metformin) fixed dose combination[2]**
Alogliptin and metformin is a FDC therapy for the treatment of type 2 diabetes, which combines 12.5 mg alogliptin and 1000 mg metformin in a single tablet, taken twice daily. *Vipdomet* is indicated in the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycemic control in adult patients, inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin
- in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone
- in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycemic control

The alogliptin and metformin fixed-dose combination is currently available in the US under the brand name *Kazano*.

**About *Incresync* (alogliptin and pioglitazone) fixed dose combination[3]**
Alogliptin and pioglitazone is a FDC therapy for the treatment of type 2 diabetes, which combines 25 mg alogliptin and 45 mg pioglitazone in a single tablet, taken once daily. *Incresync* is indicated as a second or third line treatment in adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycemic control in adult patients (particularly overweight patients) inadequately controlled on pioglitazone alone, and for whom metformin is inappropriate due to contraindications or intolerance
- in combination with metformin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in adult patients (particularly overweight patients) inadequately controlled on their maximal tolerated dose of metformin and pioglitazone

The alogliptin and pioglitazone fixed-dose combination is currently available in Japan under the brand name *Liovel* and in the US as *Oseni*.

**About type 2 diabetes**
- In 2012, 371 million people were living with type 2 diabetes worldwide. That number continues to grow and by 2030 it is estimated to rise to 552 million[15]
- In 2011, the number of people with diabetes in Europe was estimated to be 55 million[15]
- The number of type 2 diabetes patients is increasing in every country[15]
- In 2011, one in 10 deaths in adults in the Europe are attributed to diabetes, representing close to 600,000 people[15]
- Estimates indicate that more than EUR 99 billion* was spent on healthcare due to diabetes in the European region in 2011, accounting for almost one-third of global healthcare expenditures due to diabetes[15]
- Because of the chronic nature of this disease, combination therapy is almost uniformly required to maintain diabetic control over many years of therapy[16]

*Based on conversion of USD 131 billion, [15] where 1 EUR = 1.32942 USD as at 12 August 2013

**About Takeda Pharmaceutical Company Limited**
Located in Osaka, Japan, Takeda is a research-based global company with its main focus on pharmaceuticals. As the largest pharmaceutical company in Japan and one of the global leaders of the industry, Takeda is committed to strive towards better health for people worldwide through leading innovation in medicine. Additional information about Takeda is available through its corporate website, www.takeda.com.

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