Mundipharma Welcomes the New Guidelines from ESC/EASD Recommending First-Line use of Sodium-Glucose Co-transporter-2 Inhibitors for Type 2 Diabetes Patients with Cardiovascular Disease

- *The 2019 ESC (European Society of Cardiology) Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the EASD (European Association for the Study of Diabetes)[1] were presented yesterday at the ESC Congress in Paris, France*
- *The new guidelines recommend sodium-glucose co-transporter-2 inhibitors (SGLT2is) as a first-line treatment option for the management of type 2 diabetes mellitus (T2DM) patients, either drug naïve or on metformin, with atherosclerotic cardiovascular disease (ASCVD) or high/very high CV risk[1]*
- *The guidelines also recommended SGLT2is as a first-line treatment for T2DM patients who are at high risk of heart failure (HF), and for the prevention and management of chronic kidney disease (CKD) in patients who are at a high associated risk of CV disease[1]*
- *Data from cardiovascular (CV) and renal outcome trials for SGLT2is were used to inform the guidelines update. These included the positive CV outcomes data for Invokana® (canagliflozin) from the CANVAS Programme[2] and CV and CKD outcomes from the CREDENCE clinical trial[3]*
- *CV disease and CKD are major complications for patients with T2DM.[4] The risk of death from CV disease is two to six times higher in patients with T2DM than those without diabetes[4]*

CAMBRIDGE, UK: 03.09.19 – As the European distributor of Invokana® (canagliflozin) and Vokanamet® (canagliflozin and metformin), the Mundipharma network of independent associated companies welcomes the news that the sodium-glucose co-transporter-2 inhibitors (SGLT2is) class, which includes canagliflozin, has now been recommended in the newly published *2019 ESC (European Society of Cardiology) Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the EASD (European Association for the Study of Diabetes)* as a first-line treatment option for the management of patients with type 2 diabetes mellitus (T2DM), either drug naïve or on metformin, with atherosclerotic cardiovascular disease (ASCVD) or high/very high cardiovascular (CV) risk, which includes patients with other target organ damage (i.e. damage to the kidneys as predicted by important markers such as proteinuria and eGFR) and multiple other risk factors.[1] Furthermore, SGLT2is are also recommended as a first-line treatment for patients with T2DM at high risk of heart failure (HF).[1] The new guidelines were presented yesterday at the 2019 ESC Congress in Paris, France and have been published in the *European Heart Journal*.[1]

Job code: MBL/DIAB-19025
Date of preparation: September 2019

The updated guidelines took into account data from CV outcomes trials for SGLT2is which have demonstrated a range of CV benefits across the class. This includes the positive CV outcomes data for canagliflozin from the CANVAS Programme.[2]

The guidelines now recommend SGLT2is as a first-line treatment option for the prevention and management of chronic kidney disease (CKD) for patients with T2DM, who have a high associated risk of CV disease.[1] Nephroprotection has been observed in recent CV outcome trials, including the CREDENCE study, which found canagliflozin plus standard of care reduced the relative risk of the primary renal and cardiovascular outcomes compared with placebo plus standard of care.[3] Canagliflozin is currently under review by the European Medicines Agency (EMA) to extend its licence for use in the T2DM with CKD patient population.

"It is exciting to see that the recent positive results from CV outcomes trials of SGLT2is in patients with type 2 diabetes have been reflected in the updated ESC/EASD guidelines," commented Professor Antonio Ceriello, Head of Diabetes Research Department, IRCCS MultiMedica, Milan, Italy. *"It is important for clinicians to now recognise that initiating an SGLT2i, such as canagliflozin, as a first line therapy in patients with certain types of CV disease, or target organ damage, may improve long-term patient outcomes."*

Approximately 58 million people in Europe currently live with T2DM, which is set to rise to 67 million by 2045.[5] If left untreated, patients are at greater risk of developing serious health complications, such as renal disease, HF, and CV disease which is the most common cause of death for T2DM patients.[4]

"Cardiovascular disease is a major complication of type 2 diabetes which puts patients' lives at risk and is a significant burden on healthcare systems across Europe. With the new guidelines, clinicians can make the best treatment decisions and transform the standard of care for their patients." said Dr Vinicius Gomes de Lima, European Medical Affairs Lead, Mundipharma.

The updated guidelines can be viewed at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Diabetes-Pre-Diabetes-and-Cardiovascular-Diseases-developed-with-the-EASD.

-END-

Job code: MBL/DIAB-19025
Date of preparation: September 2019

Notes to the editors:

About the Guidelines[1]

The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) convened a panel to update the existing guidelines, published in 2013, on the management of diabetes, pre-diabetes and cardiovascular diseases. The updated guidelines were published in the European Heart Journal and were presented during the annual meeting of ESC in Paris, France, on the 2nd September 2019.

About Invokana®[6]

Invokana® (canagliflozin) is an oral, once-daily medication which belongs to a class of medications called sodium glucose co-transporter 2 (SGLT2) inhibitors. SGLT2 inhibitors work by inhibiting SGLT2, which promotes the loss of glucose via the urine, lowering blood glucose levels in adults with T2DM. Invokana was approved in the European Union by the European Commission in November 2013. It is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications and in addition to other medicinal products for the treatment of diabetes. Approval was based on a comprehensive global Phase III clinical trial programme.

About Vokanamet®[7]

Vokanamet® (a fixed-dose combination of canagliflozin and metformin) is approved in the European Union for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise. Vokanamet combines two oral glucose-lowering medicinal products with different and complementary mechanisms of action.

About the CANVAS Programme[2]

The CANVAS Programme (N=10,142) comprised the two large canagliflozin cardiovascular outcome trials, CANVAS and CANVAS-R, and included a pre-specified integrated analysis of these two studies to evaluate the potential for CV protection of canagliflozin in patients with T2DM who had either a prior history of CV disease or at least two CV risk factors. The integrated analysis also evaluated the effects of canagliflozin on renal and safety outcomes.

Canagliflozin met the primary outcome by significantly reducing the rates of the composite of major adverse CV events (MACE) comprised of CV mortality, non-fatal myocardial infarction (MI), or non-fatal stroke (26.9 vs. 31.5/1000 patient-years, hazard ratio (HR) 0.86; 95% confidence interval (CI 0.75-0.97; P<0.0001 for non-inferiority; P=0.0158 for superiority) compared with placebo plus standard of

care, respectively. All 3 components of MACE composite (CV death, non-fatal MI, and non-fatal stroke) exhibited point estimates of effect suggesting benefit with canagliflozin.

Adverse events reported in the CANVAS Programme were generally consistent with the known safety profile of canagliflozin. Whilst an increase in lower limb amputation and bone fractures were observed in the CANVAS Programme, this signal was not observed in further long term clinical trial data involving high risk patients.[3]

About the CREDENCE Clinical Trial[3]

The CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation) study was the first dedicated and fully recruited renal outcome trial evaluating renal and cardiovascular outcomes in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) with a sodium glucose co-transporter 2 (SGLT2) inhibitor. It was a phase 3 randomised, double-blind, event-driven, placebo-controlled, parallel-group, 2 arm multi-centre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and CKD. In particular, it compared the efficacy and safety of canagliflozin versus placebo at preventing clinically important kidney and cardiovascular outcomes in patients with T2DM and CKD when used in addition to standard of care, including a maximum tolerated daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

About the Mundipharma network

Mundipharma is a global network of privately-owned independent associated companies whose purpose is to move medicine forward. With a high performing and learning organisation that strives for innovation and commercial excellence through partnerships, we successfully transformed and diversified our European portfolio of medicines to create value for patients, payers and wider healthcare systems across important therapeutic areas such as Diabetes, Respiratory, Oncology, Pain and Biosimilars.

Invokana® and Vokanamet® are registered trademarks of Janssen

For further information please contact:

Cendrine Banerjee-Quetel

Asset Communications Associate, Mundipharma International Ltd

Email: Cendrine.Banerjee-Quetel.external@mundipharma.com

Tel: +44 (0) 1223 393 009

Job code: MBL/DIAB-19025
Date of preparation: September 2019

Abbie Bell

Senior Account Manager, Havas SO

E-mail: HavasSO-Mundipharma@havasso.com

Tel: +44 (0) 20 3196 9919

Mob: +44 7375 660 515

References:

[1] European Society of Cardiology (ESC). 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European Heart Journal* (2019);00,1-69.

[2] Neal B et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England Journal of Medicine* (2017);377:644-657.

[3] Perkovic, V. et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephrology. *The New England Journal of Medicine.* 2019; 380(24): 2295-2306.

[4] Fan, W. Epidemiology in diabetes mellitus and cardiovascular disease. *Cardiovascular Endocrinology & Metabolism*. 2017;6(1):8-16.

[5] IDF Diabetes Atlas Eighth Edition 2017. Available at: http://diabetesatlas.org/resources/2017-atlas.html. Last accessed September 2019.

[6] Invokana SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/invokana-epar-product-information_en.pdf Last accessed September 2019

[7] Vokanamet SmPC. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors 20/European_Commission_final_decision/WC500206514.pdf. Last accessed September 2019