

## XIGDUO™ XR (dapagliflozin and metformin HCl extended-release) tablets, AstraZeneca, Wilmington, DE

Clinical Executive Summary (last updated: November 2014)

Some information contained in this response may not be included in the approved Prescribing Information (PI) and is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling. Please consult the complete PI for XIGDUO XR, which may be obtained from [www.astrazeneca-us.com](http://www.astrazeneca-us.com).

### Overview of XIGDUO XR<sup>1,2</sup>

- XIGDUO XR is the only once-daily combination of a sodium-glucose cotransporter 2 (SGLT2) inhibitor and metformin (MET) extended-release (XR).
- XIGDUO XR combines two oral antihyperglycemic agents with complementary mechanisms of action that target multiple pathophysiologies associated with type 2 diabetes mellitus (T2DM).
  - Dapagliflozin (DAPA) works in the kidney by inhibiting SGLT2, reducing the reabsorption of filtered glucose, and lowering the renal threshold for glucose. This increases urinary glucose excretion.
  - MET XR works in multiple ways, including via the liver to decrease hepatic glucose production, in the intestine to reduce absorption of glucose, and in peripheral tissues to improve insulin sensitivity and increase peripheral glucose uptake and utilization.
- The combination of DAPA and MET has been evaluated in 13 Phase IIb/III placebo- and active-controlled studies that included its use as initial combination therapy in treatment-naïve patients, and as add-on to insulin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a sulfonylurea (SU).
- Clinical studies have demonstrated that XIGDUO XR is effective in reducing glycosylated hemoglobin (HbA1c), with the additional benefits of weight and blood pressure reduction, along with a low propensity to cause hypoglycemia.

**Indication<sup>1</sup>:** XIGDUO XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both DAPA and MET is appropriate.

### Limitations of Use & Dosing<sup>1</sup>

- XIGDUO XR should not be used to treat patients with type 1 diabetes or diabetic ketoacidosis.
- Healthcare providers should individualize the starting dose of XIGDUO XR based on the patient's current treatment.
- XIGDUO XR should be taken once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal side effects due to MET. Tablets must be swallowed whole and never crushed, cut, or chewed.
- Dosing should not exceed the maximum recommended daily dose of DAPA 10 mg and MET XR 2000 mg.
- Patients already taking an evening dose of MET XR should skip their last dose before starting XIGDUO XR.
- In patients with volume depletion, correcting this condition prior to initiation of XIGDUO XR is recommended.
- No dose adjustment is needed in patients with mild renal impairment (estimated glomerular filtration rate [eGFR]  $\geq 60$  mL/min/1.73 m<sup>2</sup>). Assess renal function before initiating XIGDUO XR and periodically thereafter. XIGDUO XR should not be used in patients with moderate to severe renal impairment (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>, creatinine clearance [CrCl]  $< 60$  mL/min, or end-stage renal disease).

**Clinical Data:** There have been no clinical efficacy studies conducted with XIGDUO XR; however, XIGDUO XR combination tablets are considered to be bioequivalent to the co-administration of corresponding doses of DAPA and MET XR given together as individual tablets.<sup>1</sup> Data from 3 Phase III studies and a network meta-analysis are presented below.

### DAPA Co-administration With MET XR (titrated up to 2000 mg/day) in Treatment-Naïve Patients Versus Either Agent Alone<sup>1,3</sup>

- Two 24-week, double-blind, active-controlled trials in patients with inadequately controlled T2DM (HbA1c 7.5% to 12.0%) randomized patients as follows: Study 1: DAPA 5 mg + MET XR (n=194); DAPA 5 mg + placebo (n=203); MET XR + placebo (n=201). Study 2: DAPA 10 mg + MET XR (n=211); DAPA 10 mg + placebo (n=219); MET XR + placebo (n=208).

**Reduction in HbA1c:** DAPA 5 mg + MET XR and DAPA 10 mg + MET XR demonstrated -2.1% and -2.0% reductions in HbA1c at 24 weeks from baselines of 9.2% and 9.1%, respectively. These reductions were significantly greater than monotherapy with either DAPA or MET XR in both studies ( $P < 0.0001$ ). Percent of patients treated with DAPA 5 mg + MET XR and DAPA 10 mg + MET XR that achieved an HbA1c lower than 7% at 24 weeks were 52.4% and 46.6%, respectively ( $P < 0.05$ ).

**Reduction in Total Body Weight (TBW):** DAPA 5 mg + MET XR and DAPA 10 mg + MET XR demonstrated -2.7 kg and -3.3 kg reductions in TBW at 24 weeks from baseline, respectively. These reductions were significantly greater than with either DAPA or MET XR monotherapy in Study 1 and versus MET XR monotherapy in Study 2 ( $P < 0.0001$ ).

**Reduction in Systolic Blood Pressure (SBP):** DAPA 5 mg + MET XR and DAPA 10 mg + MET XR demonstrated -2.9 mm Hg and -3.3 mm Hg reductions in SBP at 24 weeks from baseline, respectively, compared with -1.8 mm Hg and -1.2 mm Hg reductions with MET XR monotherapy in both studies.

**Occurrence of Hypoglycemia:** The frequency of hypoglycemia was  $< 5\%$  in patients treated with DAPA + MET XR or either DAPA or MET XR monotherapy in both studies. No episodes of major hypoglycemia were reported in any of the groups.

### DAPA Add-on to MET Versus Glipizide (GLIP) Add-on to MET

- In a 52-week, double-blind, active-controlled trial with a 156-week follow-up period, patients inadequately controlled on  $\geq 1500$  mg MET (HbA1c  $> 6.5\%$  to  $\leq 10.0\%$ ) were randomized to receive DAPA up-titrated to 10 mg (n=400) or GLIP up-titrated to 20 mg (n=401).<sup>1,4</sup>

**Reduction in HbA1c:** As an add-on to MET, DAPA was non-inferior in reducing HbA1c from baseline compared with GLIP. Reductions in both arms were 0.5% at week 52.<sup>1,4</sup> At 4 years, the difference between comparators in HbA1c was -0.3%, favoring DAPA + MET.<sup>5</sup>

**Reduction in TBW:** DAPA + MET significantly reduced TBW (-3.2 kg) compared with GLIP + MET (+1.4 kg) from baseline to week 52 ( $P < 0.0001$ ).<sup>1,4</sup> At 4 years, the difference between comparators in TBW was -4.38 kg, favoring DAPA + MET.<sup>5</sup>

**Reduction in SBP:** A significant comparator-adjusted reduction in SBP with DAPA + MET of -5.0 mm Hg was seen relative to GLIP + MET ( $P < 0.05$ ).<sup>1,4</sup> At 4 years, the difference between comparators in SBP was -3.67 mm Hg, favoring DAPA + MET.<sup>5</sup>

**Occurrence of Hypoglycemia:** Minor hypoglycemia occurred in 1.7% versus 36.0% of DAPA + MET and GLIP + MET patients, respectively, by week 52. Major hypoglycemia occurred in 0 patients treated with DAPA + MET and 0.7% of patients in the GLIP + MET

group.<sup>1,4</sup> Over 4 years, the proportion of patients experiencing hypoglycemia was 5.4% with DAPA + MET versus 51.5% with GLIP + MET.<sup>5</sup>

**Network Meta-analysis (NMA):**

- A systematic literature review and Bayesian NMA of 6 randomized controlled trials involving antidiabetes treatments added to MET demonstrated that DAPA, when compared with DPP-4 inhibitors, thiazolidinediones (TZDs), and SUs, offered similar HbA1c control after 1 year, with comparable or reduced risk (vs. SU) of hypoglycemia, and the additional benefit of weight loss (vs. DPP-4 inhibitor and SU). Results and 95% confidence intervals shown below were from a random effects model, which represents the best estimate based on an assessment of a *priori* model choice, statistical and clinical significance of model coefficient, model fit, and assessment of the posterior distribution of the between studies variance.<sup>6</sup>

	HbA1c (%)	Weight (kg)	Hypoglycemia (Odds Ratio)
DAPA vs. DPP-4 inhibitor	-0.08 (-0.25, 0.10)	-2.74 (-5.35, -0.10)	0.81 (0.18, 2.59)
DAPA vs. TZD	-0.02 (-0.24, 0.21)	- <sup>a</sup>	0.92 (0.09, 3.88)
DAPA vs. SU	0.00 (-0.16, 0.16)	-4.67 (-7.03, -2.35)	0.06 (0.02, 0.17)

DAPA = dapagliflozin; DPP-4 = dipeptidyl peptidase-4; SU = sulfonylurea; TZD = thiazolidinedione. <sup>a</sup>No estimate due to absence of variance for TZD trial arms.

**Pharmacodynamics:** A dose-dependent increase in the amount of glucose excreted in urine has been demonstrated within 24 hours of DAPA administration. DAPA 5 mg or 10 mg per day in patients with T2DM resulted in 70 g of urinary glucose excretion at week 12.<sup>1</sup>

**Safety:** Please see Warnings and Precautions and additional safety information, including boxed warning and common adverse reactions associated with XIGDUO XR, in the XIGDUO XR Prescribing Information.

**MET**

- XIGDUO XR has the following BOXED WARNING: **LACTIC ACIDOSIS is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, XIGDUO XR should be discontinued and the patient hospitalized immediately.**<sup>1</sup>

**DAPA**

- DAPA increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating XIGDUO XR. Renal function should be evaluated prior to initiation of XIGDUO XR and at least annually thereafter.<sup>1</sup>
- DAPA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating DAPA, particularly in patients with an eGFR <60 mL/min/1.73 m<sup>2</sup>, elderly patients, or patients on loop diuretics. Before initiating XIGDUO XR in patients with one or more of these characteristics, assessing and correcting volume status is recommended.<sup>1</sup>
- A higher incidence of hypoglycemic events was observed when agents known to cause hypoglycemia, such as insulin and insulin secretagogues, were combined with DAPA. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with XIGDUO XR.<sup>1</sup>
- Increased rates of genital mycotic infections were identified. Signs and symptoms of these events were all mild or moderate in intensity, and most events readily responded to standard treatment and rarely resulted in treatment discontinuation. Patients who had a history of recurrent genital mycotic infection were more likely to have another event while on DAPA.<sup>1,2</sup>
- Increases in low-density lipoprotein cholesterol (LDL-C) occur with DAPA. Monitor LDL-C and treat per standard of care after initiating XIGDUO XR.<sup>1</sup>
- An imbalance in bladder cancers was observed in DAPA clinical trials. XIGDUO XR should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.<sup>1</sup>

Reference(s)

- XIGDUO XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2014.
- Bristol-Myers Squibb-AstraZeneca. Background Document for the US Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee. Meeting Date, 12 Dec 2013.
- Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. *Int J Clin Pract.* 2012;66:446-456.
- Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care.* 2011;34:2015-2022.
- Del Prato S, Nauck MA, Duran-Garcia, et al. Durability of dapagliflozin vs glipizide as add-on therapies in T2DM inadequately controlled on metformin: 4-year data [poster]. Presented at: 73<sup>rd</sup> Annual Scientific Sessions of the American Diabetes Association; June 21-25, 2013; Chicago, IL. Poster 62-LB.
- Goring S, Hawkins N, Wygant G, et al. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis. *Diabetes Obes Metab.* 2014;16:433-442.