Pr forxiga (dapagliflozin)

FORXIGA® now has an indication in adults with T2D mellitus and CV risk factors or established disease.[1]

Dear Dr. [LastName],

[I am following up on our recent discussion.] / [I hope you are well.] / [It might be awhile before we meet in person, so I wanted to send you some information about FORXIGA.] As a healthcare professional, your priority at the moment is keeping your staff and patients safe from COVID-19, and I understand that you are not seeing your type 2 diabetes patients in the way you are accustomed to. I appreciate that you are taking the time to learn about the new indication for FORXIGA that is being shared with you here.

TWO INDICATIONS

For adults with T2D mellitus…

Help improve their glycemic control[1]

FORXIGA® (dapagliflozin) is indicated in monotherapy for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

FORXIGA is also indicated in adult patients with type 2 diabetes mellitus to improve glycemic control in add-on combination with metformin, a sulfonylurea, metformin and a sulfonylurea, sitagliptin (alone or with metformin) or insulin (alone or with metformin), when metformin alone or the existing therapy listed above, along with diet and exercise, does not provide adequate glycemic control.

For adults with T2D mellitus and CV risk factors or established CV disease…

Help reduce their risk of hospitalization for heart failure[1]

NEW INDICATION

FORXIGA is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of hospitalization for heart failure in adults with T2D mellitus and CV risk factors or established CV disease.

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The DECLARE-TIMI 58 study has the largest population of T2D patients with CV risk factors or established CV disease in an SGLT2i CVOT published trial to date[2*]

THE DECLARE-TIMI 58 STUDY was conducted to evaluate the effect of FORXIGA compared with placebo on CV outcomes when added to current background therapy in patients with T2D mellitus and either CV risk factors or established CV disease.[1,2]

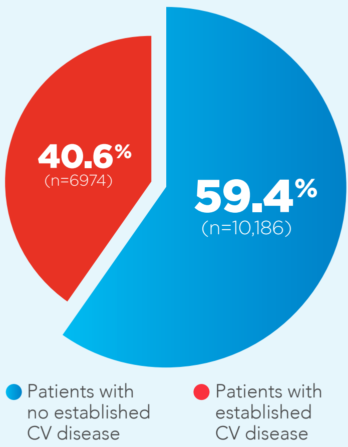
Followed patients for a mean of 4.1 years

- International, multicentre, randomized, double-blind, placebo-controlled, event-driven clinical study
- Evaluated the effect of FORXIGA vs. placebo on CV outcomes when added to current background therapy
- 8582 patients were randomized to FORXIGA 10 mg
- 8578 patients were randomized to placebo
- The primary efficacy outcomes were the composite of CV death, myocardial infarction or ischemic stroke (MACE) and the composite of hospitalization for heart failure or cardiovascular death

DECLARE-TIMI 58 PATIENT POPULATION[1]

Number of randomized patients: 17,160

Patient population[1]



All patients had T2DM and either:[1]

- At least two additional CV risk factors, without having had a CV event at baseline (primary prevention). Multiple risk factors included:
  - Age ≥55 years in men or ≥60 years in women

  and
  - One or more of: dyslipidemia, hypertension, or current tobacco use

Or

- Established CV disease (secondary prevention)

Randomization:[1]

- FORXIGA 10 mg: 8582 patients
- Placebo: 8578 patients

Other patient characteristics:[1]

- Mean duration of diabetes: 11.9 years

- Mean HbA1c: 8.3%
- History of heart failure at baseline: 10%
- Mean eGFR: 85.2 mL/min/1.73 m^2
  - eGFR <60 mL/min/1.73 m^2: 7.4%
  - eGFR >60 to <90 mL/min/1.73 m^2: 45.1%
- Micro- or macroalbuminuria at baseline (UACR ≥30 to ≤300 mg/g or >300 mg/g, respectively): 30.3%

FORXIGA demonstrated a lower rate of hospitalization for heart failure (component of the primary composite endpoint of hospitalization for heart failure or CV death; exploratory variable) **in adults with T2D and CV risk factors or established CV disease vs. placebo**[1†]

27% RRR

(2.5% vs. 3.3%) (0.8% ARR) in hospitalization for heart failure (HR 0.73; 95% CI, 0.61-0.88) *p*<0.001[1‡]

FORXIGA demonstrated a lower rate of the primary composite endpoint of CV death or hospitalization for heart failure[§] vs. placebo:[1†‡]

- **17% reduction in risk**
- **HR 0.83 (95% CI, 0.73-0.95)**
- **4.9% vs. 5.8%, respectively; *p*=0.005**

- FORXIGA was not superior to placebo for CV death (component of the primary composite endpoint of hospitalization for heart failure or CV death; exploratory variable):[1†‡]
  - HR 0.98 (95% CI, 0.82-1.17)
  - 2.9% (n=245) FORXIGA vs. 2.9% (n=249) placebo; *p*=0.83

FORXIGA IS NOT INDICATED TO REDUCE THE RISK OF CV DEATH.

Demonstrated results for the MACE primary composite endpoint (composite of CV death, myocardial infarction, and ischemic stroke) **and its components in the DECLARE-TIMI 58 study**[1†§]

Superiority of FORXIGA over placebo was not demonstrated for MACE.[1]

	PATIENTS WITH EVENTS, N (%)		
	FORXIGA 10 MG (N=8582)	**PLACEBO** (N=8578)	**HAZARD RATIO** (95% CI); *p*-value[‡]
MACE primary composite endpoint (composite of CV death, MI, ischemic stroke)	**756 (8.8%)**	**803 (9.4%)**	**0.93 (0.84, 1.03); *p*=0.172**
CV death	245 (2.9%)	249 (2.9%)	0.98 (0.82, 1.17); *p*=0.83
Myocardial infarction (MI)	393 (4.6%)	441 (5.1%)	0.89 (0.77, 1.01); *p*=0.08
Ischemic stroke	235 (2.7%)	231 (2.7%)	1.01 (0.84, 1.21); *p*=0.916

Adapted from the FORXIGA Product Monograph[1]

FORXIGA IS NOT INDICATED TO REDUCE THE RISK OF MACE, CV DEATH, MYOCARDIAL INFARCTION, AND ISCHEMIC STROKE.

Clinical use:

- Not for use in pediatrics (<18 years).
- No dosage adjustment is required in patients ≥65 years of age. FORXIGA should be used with caution in this population as a higher proportion of patients ≥65 years of age treated with FORXIGA had adverse reactions related to volume depletion and renal impairment or failure, compared to patients treated with placebo.

Contraindications:

- Patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease (ESRD) or patients on dialysis.

Most serious warnings and precautions:

- **Diabetic ketoacidosis:** Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with FORXIGA (dapagliflozin) and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL). Some cases of DKA have been fatal. If DKA is suspected, regardless of blood glucose level, patients should discontinue FORXIGA treatment and be assessed for DKA immediately. If DKA is diagnosed, FORXIGA should be discontinued immediately.
  - FORXIGA should not be used for the treatment of DKA or in patients with a history of DKA.
  - FORXIGA is not indicated, and should not be used, in patients with type 1 diabetes.

Other relevant warnings and precautions:

- DKA: Interruption of treatment with FORXIGA should be considered in type 2 diabetes patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illness. Patients with conditions that can precipitate DKA while taking FORXIGA should be monitored closely. Caution should also be taken when reducing the insulin dose in patients requiring insulin.
- Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances
- Risk of hypoglycemia when used in combination with insulin or insulin secretagogues
- Dose-related LDL-C increases; monitor LDL-C levels
- Increased mean hemoglobin/hematocrit and frequency of patients with abnormally elevated values of hemoglobin/hematocrit
- Increased risk of genital mycotic infections and urinary tract infections (including urosepsis and pyelonephritis)
- Risk of necrotizing fasciitis of the perineum (Fournier's gangrene)
- Not recommended in severe hepatic impairment
- Renal function abnormalities and acute kidney injury, including acute renal failure. Patients with hypovolemia may be more susceptible to these changes
- Renal function should be assessed prior to initiation of FORXIGA and regularly thereafter, with more frequent monitoring in patients whose eGFR decreases to <60 mL/min/1.73 m^2
- Not for use in pregnant or nursing women
- Patients taking FORXIGA will test positive for glucose in their urine

For more information:

Please consult the Product Monograph at www.azinfo.ca/forxiga/pm367 for important information relating to adverse reactions, drug interactions and dosing. The Product Monograph is also available by calling 1-800-668-6000.

DOWNLOAD THE FORXIGA PRODUCT MONOGRAPH AT FORXIGA.CA

Sincerely,

[Rep Name]
[Rep Email]
[Rep Mobile number]
AstraZeneca Canada Inc.

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* Comparative clinical significance has not been established.

† The primary efficacy outcomes were MACE (a composite of CV death, myocardial infarction or ischemic stroke) and the composite of hospitalization for heart failure or cardiovascular death (the components of the composite endpoints were exploratory variables). (Dual primary efficacy endpoints may be used when success on either endpoint could independently support a conclusion of effectiveness. The dual primary efficacy endpoints in DECLARE were tested independently and in parallel. Type 1 error was controlled by splitting the α between the dual primary endpoints.)

‡ Hazard ratio, CI, and p-values for each efficacy parameter were calculated from Cox proportional hazards model based on time to first occurrence, stratified by baseline CV risk and hematuria with treatment as a model term.

Superiority versus placebo for hospitalization for heart failure or CV death, and superiority versus placebo for MACE were tested in parallel following closed testing procedure at α=0.0231 (two-sided). As the composite of hospitalization for heart failure and CV was statistically significant, the full α was recycled to test MACE at α=0.0462 (two-sided).

§ Full analysis set.

ARR: absolute risk reduction; BP: blood pressure; CI: confidence interval; CV: cardiovascular; CVOT: cardiovascular outcomes trial; DECLARE: Dapagliflozin Effect on Cardiovascular Events; HR: hazard ratio; MACE: major adverse cardiovascular events; RRR: relative risk reduction; SGLT2i: sodium-glucose co-transporter 2 inhibitor; T2D: type 2 diabetes; TIMI: Thrombolysis in Myocardial Infarction.

Pr forxiga®
(dapagliflozin)

REFERENCES: 1. Product FORIXGA Monograph. AstraZeneca Canada Inc. April 1, 2020. **2.** Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347-357.

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