

Brief Therapeutic Update from PES Drugs and Therapeutics Committee

Jardiance® (empagliflozin) and

Synjardy® (empagliflozin and metformin hydrochlorothiazide)

Jardiance® (empagliflozin) and Synjardy® (empagliflozin and metformin hydrochlorothiazide) were approved by the FDA for treatment of type 2 diabetes mellitus in children ≥ 10 years of age on June 20, 2023.[1] The novel active ingredient in Jardiance® and Synjardy® is empagliflozin, a sodium-glucose co-transporter 2 inhibitor (SGLT2 inhibitor) which blocks renal re-uptake of glucose, promoting glycosuria and lowering blood glucose levels. Jardiance® is available at 10 mg (initial dose) and 25 mg tablets. Synjardy® is available for twice daily dosing as 5 mg empagliflozin/500 mg metformin, 5 mg empagliflozin/1000 mg metformin, 12.5 mg empagliflozin/500 mg metformin, and 12.5 mg empagliflozin/1000 mg metformin.

Empagliflozin was approved for pediatric use based on the results of the industry-sponsored DINAMO study, an international multicenter randomized double-blinded, placebo-controlled, parallel group trial.[2] The trial included 158 overweight (BMI $\geq 85^{\text{th}}$ percentile) subjects ages 10-17 years with diagnosis of type 2 diabetes mellitus for ≥ 8 weeks and HbA1c 6.5-10.5%. Subjects were excluded if taking any anti-diabetic medication other than metformin or insulin within 8 weeks. They were evenly randomized to take either empagliflozin 10 mg, linagliptin 5 mg (a dipeptidyl peptidase-4 inhibitor), or placebo daily for 26 weeks. Those in the empagliflozin group who failed to achieve a HbA1c $< 7\%$ by week 12 were further randomized to either continue 10 mg or increase to 25 mg. The safety of empagliflozin was assessed through week 52 of the extension phase.[2]

At 26 weeks, the primary outcome, adjusted mean HbA1c change, for the empagliflozin group compared to placebo was -0.84% (95%CI -1.50 to -0.19 , $p = 0.012$), with greater change of -1.93% (-3.35 to -0.05) in those with higher baseline HbA1c of $> 9.0\%$. However, the mean HbA1c change from baseline to 26 weeks was not significant for the pooled empagliflozin group [-0.17% (95% CI -0.64 to 0.31)] or the linagliptin group [$+0.33\%$ (95% CI -0.13 to 0.79)].

The pooled empagliflozin group had a significant reduction in the adjusted mean fasting glucose of -19.48 mg/dL (95% CI -36.39 to -2.57) at 26 weeks, whereas the placebo and linagliptin groups did not show significant change. Eleven percent of placebo group, 10% of pooled empagliflozin group, and 8% of linagliptin group required insulin rescue therapy by week 26.[2]

Hypoglycemia was the most frequent adverse event and was more common in the empagliflozin (23%) and linagliptin groups (19%) compared to placebo (9%) at 26 weeks, but there was no severe hypoglycemia requiring assistance. Urinary tract infections were more common in the empagliflozin group (6%) compared to placebo or linagliptin (2% for both). Genital infections did not differ between empagliflozin and placebo (2%). There were no instances of pyelonephritis, necrotizing fasciitis, or lower limb amputations. There was also no diabetic ketoacidosis in the two active medication groups by 26 weeks.[2]

References:

1. U.S. Food and Drug Administration. *FDA approves new class of medicines to treat pediatric type 2 diabetes.*; 2023. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-class-medicines-treat-pediatric-type-2-diabetes#:~:text=Today%2C%20the%20U.S.%20Food%20and,older%20with%20type%20%20diabetes.> Accessed August 1, 2023.

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2. Laffel LM, Danne T, Klingensmith GJ, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *Lancet Diabetes Endocrinol.* 2023;11(3):169-181. doi:10.1016/S2213-8587(22)00387-4

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