POST-AUTHORISATION SAFETY STUDY INFORMATION

Title	Post-authorisation Observational Study: Comparison of the Risk of Acute Liver Injury Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments
Version identifier of the final study report	Version 1.0
Date of last version of study report	09 November 2020
European Union Post-Authorisation Studies Register number	Acute liver injury: ENCEPP/SDPP/12110
Active substance	A10BX09 (dapagliflozin) A10BD15 (metformin and dapagliflozin) A10BD21 (saxagliptin and dapagliflozin)
Medicinal product	Dapagliflozin (Edistride, Forxiga [EU]; Farxiga [US]) Dapagliflozin + metformin (Ebymect, Xigduo) Dapagliflozin + saxagliptin (Qtern)
Product reference	Forxiga EU/1/12/795/001-010 Edistride: EU/1/15/1052/001-010 Xigduo: EU/1/13/900/001-012 Ebymect: EU/1/15/1051/001-012 Qtern: EU/1/16/1108/001-004
Procedure number	Forxiga: EMEA/H/C/002322 Edistride: EMEA/H/C/004161 Xigduo: EMEA/H/C/002672 Ebymect: EMEA/H/C/004162 Qtern: EMEA/H/C/004057
Marketing authorisation holder(s)	AstraZeneca AB
Is this a joint post-authorisation safety study (PASS)?	No

Research question and objectives	This study was a multinational cohort study to estimate the risk of acute liver injury in patients with type 2 diabetes mellitus (T2DM) who are new users of dapagliflozin compared with those who are new users of antidiabetic drugs (ADs) other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. The main study objective was to compare, by insulin use at the date of the index episode, the incidence of hospitalisation for acute liver injury among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.
Country/countries of study	United Kingdom (UK) United States of America (US)
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ABSTRACT

Title: Post-authorisation Observational Study: Comparison of the Risk of Acute Liver Injury Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments

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Date: 09 November 2020

Keywords: Diabetes mellitus type 2, dapagliflozin, acute liver injury

Rationale and background: Post-authorisation safety study (PASS) evaluating risk of acute liver injury in real-world use of dapagliflozin.

Research question and objectives: The primary objective was to compare, by insulin use at the date of the index episode, the incidence of "hospitalisation for acute liver injury" (hereafter, "ALI") among patients with type 2 diabetes mellitus (T2DM) who were new users of dapagliflozin compared with that of patients with T2DM who were new users of antidiabetic drugs (ADs) other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. Additional analyses were also conducted on the overall exposure cohorts without stratification by insulin use at the date of the index episode.

Secondary objectives were to (1) compare baseline characteristics of both exposure groups and (2) examine potential risk factors for ALI if an increased risk was found with dapagliflozin new use compared with new use of other ADs.

Study design: Non-interventional cohort study using data from three longitudinal, population-based data sources. The study cohorts were defined by new use of an eligible study medication (ie, new use of dapagliflozin or comparator AD). The date of prescription or dispensing of this medication was considered the date of the index episode if all study eligibility criteria were met. The unit of analysis was the index episode. A single patient could have multiple index episodes if a different comparator AD had been initiated on a different date, the eligibility criteria were met at the time of the new index episode, and the episodes did not overlap. Comparator AD index episodes were randomly matched—by calendar year of the index episode, age, sex, and geographic region—to each dapagliflozin index episode in the following ratios of comparator AD to dapagliflozin: up to 6 to 1 in the Clinical Practice Research Datalink (CPRD) and up to 15 to 1 in the HealthCore Integrated Research Database (HIRD®) and Medicare.

Propensity score trimming and stratification were used to adjust for multiple possible confounding variables. Descriptive analyses were conducted before and after propensity score trimming on the overall sample (with insulin use groups combined) and were stratified by

concomitant insulin use at the date of the index episode. Incidence and comparative analyses were conducted on the sample after propensity score trimming.

Crude and propensity score–adjusted incidence rates of ALI were calculated separately for dapagliflozin-exposed and comparator AD–exposed person-time for each insulin use group and for the overall sample not stratified by insulin use. Incidence rate ratios (IRRs) compared the incidence of ALI in dapagliflozin index episodes with that of comparator AD index episodes. Adjusted IRRs were calculated using Mantel-Haenszel methods from propensity score–stratified IRRs for each insulin use group and for the overall sample.

Due to very small numbers for the analyses stratified by insulin use at the index episode, particularly in the insulin use group in all data sources, and a lack of meaningful results in the stratified analyses, the text of this report focuses on the analyses performed overall without stratification by insulin use at the index episode.

Setting: The study used data from CPRD in the United Kingdom and the HIRD and Medicare in the United States of America. The study period began the day after regulatory approval of dapagliflozin in each country and ended at the last date of observation available at the time of data extraction in each data source.

Subjects and study size, including dropouts: After applying exclusion criteria, after matching and before propensity score trimming, the number of dapagliflozin index episodes in each data source in the overall cohort (with both insulin use groups combined) was as follows: CPRD, 10,466; the HIRD, 17,187; and Medicare, 13,280. After propensity score trimming, the number of dapagliflozin index episodes in each data source in the overall cohort was as follows: CPRD, 9,027; the HIRD, 15,217; and Medicare, 11,332. The number of person-years of dapagliflozin and comparator AD exposure, respectively, during the study period in the propensity score–trimmed cohorts was 10,315 and 91,740 in the HIRD, and 6,756 and 106,273 in Medicare; in CPRD, the person-years of dapagliflozin exposure were not reportable due to CPRD's small cell suppression policy and the comparator AD exposure group had 28,950 person-years.

Variables and data sources: The occurrences of ALI were identified with electronic algorithms. Validation of provisional cases identified by the electronic algorithms was performed in the three data sources.

The primary exposure was newly initiated dapagliflozin. Comparator AD exposure was defined as new initiation of an eligible AD, which did not include SGLT2 inhibitors or monotherapy with insulin, metformin, or sulfonylurea.

Potential confounding variables assessed at baseline were medical conditions related to diabetes severity, other medical comorbidities, selected medications, lifestyle factors as available in each data source, and health care resource utilisation.

Results: Before propensity score trimming, there were some relevant differences in baseline characteristics at the index episode when comparing patients presenting with episodes of dapagliflozin to patients presenting with episodes of comparator AD. The following differences were observed in all data sources: patients on dapagliflozin had greater use of concomitant insulin; greater use of previous AD classes; fewer emergency department visits or hospitalisations; higher HbA1c (glycated haemoglobin) levels or higher number of HbA1c tests; and in CPRD, more frequent obesity and longer time since diagnosis of T2DM. After propensity score trimming and stratification, good balance was observed between exposure groups in the overall sample and in the two insulin use groups for most covariates for all data sources, as indicated by absolute standardised difference values less than 0.20.

After propensity score trimming, the mean age at baseline was as follows: CPRD—58 years in both exposure groups; the HIRD—52 years in both index exposure groups; and Medicare—70 years in both index exposure groups. The percentage of index episodes with concomitant insulin was as follows: CPRD—10.6%, dapagliflozin; 5.3%, comparator AD; the HIRD—13.5%, dapagliflozin; 11.1%, comparator AD; and Medicare—16.2%, dapagliflozin; 13.5%, comparator AD. The percentage of index episodes with one or more drugs with a known association with liver injury at baseline was as follows: CPRD—91.7%, dapagliflozin; 90.3%, comparator AD; the HIRD—87.4%, dapagliflozin; 86.4%, comparator AD; and Medicare—81.4%, dapagliflozin; 83.0%, comparator AD.

The estimated positive predictive value of the electronic algorithm to identify cases of ALI was 56.3%% (95% confidence interval [CI], 29.9%-80.2%) in CPRD, 50.5% (95% CI, 40.6%-60.4%) in the HIRD, and 49.2% (95% CI, 39.9%-58.4%) in Medicare.

The overall adjusted incidence rate per 1,000 person-years, not stratified by insulin use at the index episode, for dapagliflozin and comparator AD index episodes, respectively, was 0.37 (95% CI, 0.10-0.93) and 0.62 (95% CI, 0.27-1.11) in CPRD, 1.36 (95% CI, 0.74-2.28) and 1.83 (95% CI, 1.55-2.15) in the HIRD, and 1.92 (95% CI, 1.02-3.29) and 1.70 (95% CI, 1.42-2.02) in Medicare. The overall adjusted IRR estimates in CPRD (0.63; 95% CI, 0.21-1.93) and the HIRD (0.74; 95% CI, 0.43-1.28) were below the null value, and the adjusted IRR estimate in Medicare was slightly above the null value (1.12; 95% CI, 0.63-1.99). All adjusted IRR estimates were imprecise as indicated by the wide 95% CIs. The overall pooled estimate across all three data sources for the adjusted IRR for ALI was 0.85 (95% CI, 0.59-1.24). In a sensitivity analysis extending the risk window from 30 days to 90 days, the adjusted IRR estimate was 0.56 (95% CI, 0.19-1.69) in CPRD, 0.74 (95% CI, 0.45-1.21) in the HIRD, and 1.11 (95% CI, 0.66-1.86) in Medicare, similar to the primary analysis in all data sources.

Discussion: The results of this final analysis suggest a null or slightly inverse association between hospitalisation for acute liver injury and dapagliflozin exposure compared with exposure to other ADs in the overall sample not stratified by insulin use at the index episode.

However, the results were inconclusive due to a small number of ALI events in all data sources, resulting in imprecise effect estimates. The adjusted IRR estimate for the overall sample pooled across the three data sources was below the null value, with an upper bound of the 95% CI below 2.0, which is compatible with published results from a randomised clinical trial (Wiviott et al., 2018) and do not suggest a strong increased risk of ALI. In results stratified by insulin use at the index episode, the point estimate for the adjusted IRR in Medicare was elevated in the insulin users group, but with a very wide 95% CI. Results of various sensitivity analyses were largely consistent with the results from the primary analysis but were imprecise. It is unlikely that an independent unmeasured confounder would cause enough bias to mask a true harmful association of ALI with dapagliflozin.

Marketing Authorization Holder(s): AstraZeneca AB

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Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018 Nov 10: doi: 10.1056/NEJMoa1812389. doi:http://dx.doi.org/10.1056/NEJMoa1812389.