Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE® Tablets			
Name of active ingredient: Empagliflozin			
Report date: 18 MAR 2025	**Study number:** 1245.286	**Version/Revision:** Version 1.0	**Version/Revision date:** NA
Title of study:	Post Marketing Surveillance on Long Term Drug Use of JARDIANCE® Tablets in Patients with chronic heart failure in Japan		
Keywords:	JARDIANCE® Tablets, Japan, PMS, Chronic Heart Failure (CHF)		
Rationale and background:	In Japan, post-approval execution of Post Marketing Surveillance is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and effectiveness data for re-examination. Re-examination period is defined by J-PMD Act. Four years after approval of additional indication, results of Post Marketing Surveillance (PMS) need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW). Collected data from PMS was included in the Japanese periodic safety reports and submitted to MHLW on designated dates until the end of re-examination period.		
Research question and objectives:	Study objective was to investigate the safety and effectiveness of long-term daily use of JARDIANCE® Tablets in patients with CHF under real-world use.		
Study design:	Cohort study Non-interventional, single arm study based on newly collected data Patients were observed for up to 52 weeks after start of the treatment with JARDIANCE® Tablets or until discontinuation of administration.		
Setting:	Sites throughout entire country were equally listed according to the size of the hospitals or general clinics at which JARDIANCE® Tablets were available for prescription. Planned number of sites: Approximately 200 Sites (including cardiovascular [CV] internal medicine)		

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	A medical representative explained the objective and design of this study to investigators at each study site and concluded a written contract with the head of the study site (e.g., hospital director). This study was conducted in 146 centres in Japan. Study period: April 2022 – Jun 2024 Enrollment period: April 2022 – Mar 2023		
Subjects and study size, including dropouts:	Inclusion criteria - Patients with CHF who are prescribed with JARDIANCE® Tablets in Japan. - Patients who have never been treated with Empagliflozin (including treatment for type 2 diabetes mellitus [T2DM]) before enrolment. Exclusion criteria None Patient disposition In this PMS, a total of 1200 patients were registered. Of the 1200 patients who registered, 9 patients were registered only but their case report forms (CRFs) were not collected. CRFs were collected from 1191 patients. All the 1191 patients for which CRFs were collected received JARDIANCE treatment.		
Variables and data sources:	Outcomes: Primary outcome: - Incidence of adverse drug reactions (ADRs) (focus on hypoglycaemia, the events relevant to volume depletion, influence of ketone body increased / ketoacidosis, renal impairment) Secondary outcome: - Incidence of all-cause death - Incidence of CV death - Incidence of hospitalizations for heart failure (HF) Further outcome: Other safety outcomes; - Incidences of serious adverse events (SAEs) - Time to all-cause death, CV death and hospitalization for HF - Change from baseline in eGFR over time		

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	- Baseline characteristics <u>Data Sources</u> Patients' data were collected by electronic CRF on Electronic Data Capture (EDC) system		
Results:	The safety set included 1166 patients and the effectiveness set included 1165 patients. <u>Baseline characteristics</u> In the safety set, 60.98% of patients were men. A total of 81.05% (945 patients) were aged 65 and above, while 18.95% (221 patients) were under 65. Among them, 60.21% (702 patients) were 75 years or older. 20.24% (236 patients) were inpatients, while 79.76% (930 patients) were outpatients. For the indication of CHF, 99.91% (1165 patients) were reported as having CHF, and 0.09% (1 patient) was reported as not having CHF (initially diagnosed as CHF but later diagnosed as respiratory disease). The duration of HF was ≤1 year for 387 patients (33.19%), >1 to 5 years for 167 patients (14.32%), >5 to 10 years for 87 patients (7.46%), >10 years for 81 patients (6.95%), and unknown for 444 patients (38.08%). A total of 399 patients (34.22%) had the concomitant disease of T2DM, while 765 patients (65.61%) did not, and unknown for 2 patients (0.17%). The duration of T2DM was ≤1 year for 20 patients (5.01%), >1 to 5 years for 29 patients (7.27%), >5 to 10 years for 31 patients (7.77%), >10 years for 42 patients (10.53%), and unknown for 277 patients (69.42%). A total of 98.37% (1147 patients) had any concomitant diseases, whereas 1.29% (15 patients) did not and 0.34% (4 patients) was unknown. Concomitant medication was present in 92.62% (1080 patients), while 5.92% (69 patients) did not have any, and 1.46% (17 patients) was unknown. A total of 43.22% (504 patients) had concomitant therapy (exercise therapy, diet therapy or water intake management), 50.00% (583 patients) did not have concomitant therapy, and 6.78% (79 patients) was unknown. <u>Exposure</u> A total of 58.92% (687 patients), were treated with JARDIANCE for over 52 weeks. Other patients were treated for 40 to 52 weeks (16.98%, 198 patients), 0 to 12 weeks (11.66%, 136 patients), 12 to 26 weeks (6.52%, 76 patients), and 26 to 40 weeks (5.83%, 68 patients). A total of 98.28% (1146 patients) received regular dosage and administration. In contrast, 1.72% (20 patients) had irregular dosage and administration.		

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	Primary outcome, Safety summary Of the safety set including 1166 patients, 61 patients (5.23%, 61/1166 patients) experienced at least 1 ADR. The most frequently reported ADRs (in more than 2 patients) throughout the PMS were dehydration (0.69%, 8/1166 patients), blood pressure decreased (0.51%, 6/1166 patients), urinary tract infection (0.43%, 5/1166 patients), hypotension and glucose urine (0.34%, 4/1166 patients each), dizziness (0.26%, 3/1166 patients), cystitis, pyelonephritis, hypoglycaemia, taste disorder, constipation, pruritus, rash, renal impairment, thirst, and weight decreased (0.17%, 2/1166 patients each). The frequency of ADR was highest at 0 to <12 weeks (2.23%, 26/1166 patients), followed by 12 to <26 weeks (1.64%, 17/1034 patients) and 26 to <40 weeks (0.62%, 6/962 patients). Compared to the JARDIANCE duration treatment of >0 to 12 weeks, the frequency of ADRs was lower in the durations of >40 to 52 weeks and >52 weeks, indicating that there was no increase in the frequency of ADRs with long-term treatment. For serious ADRs, 12 patients (1.03%) experienced at least 1 serious ADRs. The reported serious ADRs were dehydration (0.34%, 4/1166 patients), pyelonephritis and urinary tract infection (0.17%, 2/1166 patients each). All-cause death was reported for 30 patients (2.57%). AEs leading to CV death were reported for 9 patients (0.77%). AEs leading to hospitalization for HF were reported for 25 patients (2.14%). AEs leading to the discontinuation of the treatment were reported in 78 patients (6.69%). The most frequently reported AEs leading to discontinuation were urinary tract infection and cardiac failure (0.34%, 4/1166 patients each), followed by COVID-19, colon cancer and dehydration (0.26%, 3/1166 patients each). The categories for which the 95% confidence interval (CI) of the odds ratio for the ADRs frequency by patients' demographics/baseline characteristics did not include the value 1 were the following: Age class, Previous hospitalizations for HF, Previous medication for HF (Potassium - sparing diuretic, Other diuretic), Previous medication for T2DM (GLP 1 receptor agonist), Concomitant medication for HF (ARNI, Potassium - sparing diuretic), Concomitant medication for T2DM (SGLT2 inhibitor), Duration of JARDIANCE treatment class.		

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	In the PMS, hypoglycaemia, events relevant to volume depletion, influence of ketone body increased / ketoacidosis and renal impairment were listed as the priority survey items. The reported priority survey items included hypoglycaemia (0.17%, 2/1166 patients), events relevant to volume depletion (1.54%, 18/1166 patients), renal impairment (0.26%, 3/1166 patients). No ADRs of influence of ketone body increased / ketoacidosis were reported. No patients under 15 years and no pregnant women were enrolled in this PMS. The frequency of ADRs was 5.93% (56/945 patients) in elderly patients (65 years and older), compared to 2.26% (5/221 patients) in non-elderly patients (under 65 years old), indicating a higher frequency of ADRs in the elderly patients. The frequency of ADRs was higher in patients with renal dysfunction (5.35%, 58/1085 patients) than that in patients without renal dysfunction (2.33%, 1/43 patients). The frequency of ADRs was similar between patients with and without hepatic dysfunction 5.10% (8/157 patients) in patients with hepatic dysfunction versus 5.28% (52/985 patients) in patients without hepatic dysfunction. <u>Secondary outcomes</u> In the effectiveness set of 1165 patients, there were 30 all-cause death cases: an incidence rate of 3.01 deaths per 100 person-years (95% CI: 2.03-4.29 deaths per 100 person-years). CV death was observed in 9 patients, accounting for an incidence rate of 0.90 deaths per 100 person-years (95% CI: 0.41-1.71). Additionally, 25 patients experienced hospitalization for HF, accounting for an incidence rate of 2.53 hospitalizations per 100 person-years (95% CI: 1.64-3.74). <u>Further outcomes</u> In the safety set of 1166 patients, incidence of SAEs was 12.69% (148 patients). Time to all-cause death, CV death and hospitalization for HF were plotted in Kaplan-Meier estimate. The mean eGFR from baseline to Week 52 was generally maintained. The interim analyses were not performed.		
Discussion:	There was no notable difference in the safety profile observed in the PMS and the information provided in the Japanese package insert. The study does not indicate any changes on Risk and Benefit concerning JARDIANCE® Tablets treatment.		

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Names and affiliations of principal investigators:	[redacted]		