



Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance® Tablets 10 mg, 25 mg			
Name of active ingredient: EMPAGLIFLOZIN			
Report date: 25 July 2017	Study number: 1245.98	Version/Revision: Version 3.0	Version/Revision date: 13 Dec 2023
Title of study:	Post Marketing Surveillance in Japan on Drug Use of JARDIANCE® Tablets in Elderly Patients with type 2 Diabetes Mellitus		
Keywords:			
Rationale and background:	<p>In Japan, post-approval execution of post marketing surveillance (PMS) is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and efficacy data for re-examination. Re-examination period is defined by J-PMDA Act. Eight years after approval of a new substance, results of 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).</p> <p>The reason for selecting elderly patients for this surveillance was that elderly patients were known for a risk of volume depletion. A follow up period of 1 year included the summer time, and therefore, it enabled to evaluate the safety related to dehydration in the summer. Also, adverse drug reactions related to urinary tract infection and genital infection that were commonly associated with sodium-dependent glucose co-transporter-2 (SGLT-2) inhibitor had to be particularly monitored for in elderly patients who were vulnerable to infection in general; which was another reason for selecting elderly patients for this surveillance.</p>		
Research question and objectives:	Study objectives were to investigate the safety and efficacy of daily use of JARDIANCE® Tablets in Japanese elderly patients with type 2 diabetes mellitus.		
Study design:	<p>Cohort study</p> <p>Non-interventional, prospective, observational, single arm based on new data collection</p> <p>Patients with type 2 diabetes mellitus who had never received JARDIANCE® Tablets and started taking JARDIANCE® Tablets within 3 months after launch were enrolled in the surveillance.</p> <p>Patients were observed for up to 52 weeks (approximately 12 months) after start of the treatment with JARDIANCE® Tablets or at premature discontinuation and dropout.</p>		

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	Descriptive statistics were summarised for safety and efficacy. A mixed model repeated measures analysis was performed for haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) over time.		
Setting:	All elderly patients at the sites making contracts were registered during the enrolment period (3 months after launch). The patients' data were collected retrospectively since the date of contract. This study was conducted in 114 centers in Japan. Study period: February 2015 – September 2016 Enrolment period: February 2015 – May 2015		
Subjects and study size, including dropouts:	Male and female elderly patients (age 65 and over) with type 2 diabetes mellitus who had never been treated with JARDIANCE® Tablets before the enrolment and started taking JARDIANCE® Tablets within 3 months after launch in Japan.		
Variables and data sources:	<p>Outcomes:</p> <p><u>Primary outcome:</u> Incidences of adverse drug reactions (ADRs)</p> <p><u>Secondary outcomes:</u> Change from baseline in HbA1c to the last observation on treatment Change from baseline in FPG to the last observation on treatment</p> <p><u>Further outcomes:</u> Change from baseline in HbA1c at Week 26 Occurrence of efficacy response (HbA1c at the baseline of $\geq 7.0\%$, HbA1c at the baseline of $\geq 6.5\%$ become HbA1c under treatment of $< 7.0\%$, HbA1c under treatment of $< 6.5\%$ at Week 26) Occurrence of relative efficacy response (HbA1c lowering by at least 0.5% at Week 26) Change from baseline in FPG at Week 26 Incidences of serious adverse events (SAEs) Incidences of priority survey items</p> <p><u>Others: baseline characteristics</u></p>		

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	<p>Variables: Demographics Medical history/baseline conditions Previous/concomitant therapies Jardiance administration Vital signs and laboratory test Adverse event</p> <p><u>Data sources:</u> Patients data were gathered by electronic Case Report Form on electronic data capture (EDC)</p>		
Results:	<p>In this PMS, a total of 417 patients were entered in Japan. Of the 417 patients enrolled and treated, 414 and 407 patients were included in the safety and the efficacy sets, respectively. The prematurely discontinued patients before 52 weeks administration were 217 (52.0%). At the site with the largest number of registered patients, 150 of 151 patients (99.34%) were discontinued.</p> <p><u>Baseline characteristics</u> In the safety set, 58.94% of patients were male and 41.06% of patients were female. The mean age was 71.8 years (range: 65 to 88) and 123 patients (29.71%) being to “75 years old or over”. The mean body mass index (BMI) and weight were 25.38 kg/m² and 64.49 kg, respectively. The mean baseline estimated glomerular filtration (eGFR) was 71.65 mL/min/1.73m². There were no patients with moderate or severe hepatic impairment.</p> <p>All patients were diagnosed as Type 2 diabetes mellitus with mean disease duration of 13.11 years and 38.41% of the patients had diabetes for more than 10 years before they were enrolled in this study. Baseline HbA1c values in 177 patients (42.75%) were <7.0%. The mean baseline FPG was 139.7 mg/dL.</p> <p>Of the 414 patients analysed for safety, 144 patients (34.78%) were treated with antidiabetic drugs before starting administration of JARDIANCE® Tablets. The mean baseline HbA1c was 7.46%.</p>		

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<p>The mean treatment duration of JARDIANCE® Tablets was 225.2 days. Twelve (2.90%) patients starting at lower dosages (10 mg) of JARDIANCE® Tablets increased to 25 mg. The mean duration at the time of dose increase was 121.8 days.</p> <p><u>Primary outcome</u></p> <p>Eighty five patients (20.53%) experienced at least 1 ADR throughout the PMS. The frequently reported ADRs in at least 1% of patients were pollakiuria (7 patients, 1.69%), nocturia (6 patients, 1.45%), asthenia, cystitis and thirst (5 patients, 1.21% each).</p> <p><u>Safety summary</u></p> <p>A total of 91 patients (21.98%) experienced at least 1 AE throughout the PMS. Additional AEs that were not reported as ADR were asteatosis, atrial flutter, benign prostatic hyperplasia, bronchitis, gastric ulcer haemorrhage, gastroesophageal reflux disease, hepatic cirrhosis, nasopharyngitis, obesity and upper respiratory tract inflammation. They were reported from 1 patient each. The most AEs were mild or moderate in intensity. Severe AEs were reported in 6 patients.</p> <p>Six SAEs were reported in 6 patients (1.45%). Of these, 3 (in 3 patients) were considered drug-related (age-related macular degeneration, stress cardiomyopathy, and pneumonia).</p> <p>Of these, 3 (in 3 patients) were reported as not related to JARDIANCE® Tablets (blood glucose increased, atrial flutter, and hepatic cirrhosis). One patient died from worsening of a pre-existing hepatic cirrhosis.</p> <p>ADRs leading to the discontinuation of JARDIANCE® Tablet were reported in 65 patients (15.70%). The frequently reported ADRs leading to discontinuation (at least 1%) were nocturia and pollakiuria (6 patients, 1.45% each), thirst and cystitis (5 patients, 1.21% each).</p> <p>The reported priority survey items were polyuria/pollakiuria (13 patients, 3.14%), urinary tract infection (6 patients, 1.45%), hypoglycaemia (4 patients, 0.97%), volume depletion (dehydration), and liver injury (2 patients, 0.48% each), cardiovascular event (stress cardiomyopathy),</p>			

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<p>renal impairment, and the adverse events related to an increase in ketone (1 patient, 0.24% each).</p> <p>From these events, two were reported as SAE, 1 liver injury was reported as not related to JARDIANCE® Tablets and 1 cardiovascular event was reported with stress cardiomyopathy related to the treatment with JARDIANCE® Tablets.</p> <p>Genital infection, diabetic ketoacidosis, bone fracture, malignancy, and weight decreased did not occur throughout the PMS.</p> <p><u>Secondary outcomes</u></p> <p>The mean change in HbA1c (%) from baseline at the last observation was -0.36% (95%CI=-0.46 to -0.26). The mean change in FPG (mg/dL) from baseline at the last observation was -8.4 mg/dL (95%CI=-14.2 to -2.6). The data show a clinically relevant reduction in HbA1c and FPG.</p> <p><u>Further outcomes</u></p> <p>The mean change of HbA1c (%) from baseline at Week 26 was -0.68%. The mean change of FPG (mg/dL) from baseline at Week 26 was -14.1 mg/dL. The data show a clinically relevant reduction. Throughout the observation period during the PMS, mean HbA1c values were lower than the baseline value and decreases from baseline at the each time point were observed with the mean changes ranging -0.26 to -0.68%. Also FPG value recorded lower than the baseline value and decreases from baseline at the each time point were observed with the mean changes ranging -6.1 to -19.5 mg/dL.</p> <p>Forty patients (32.79%) and 26 patients (17.93%) were classified as responders with HbA1c at the baseline of $\geq 7.0\%$ and $< 6.5\%$ at Week 26, respectively. The responders with HbA1c lowering by 0.5% or more at Week 26 were 89 patients (53.94%).</p>			

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Discussion:	<p>The PMS results showed safety, efficacy and tolerability in daily use of JARDIANCE® Tablets in Japanese elderly patients with type 2 diabetes mellitus.</p> <p>The reported related AEs are in line with the safety profile of Empagliflozin and the experience from the Empagliflozin clinical trials.</p> <p>The reported SAEs do not provide information about a potential causal association with JARDIANCE® Tablets. Overall the results do not raise a safety concern.</p> <p>During the study period, no new safety measure was required such as label change or additional risk minimization based on the study results.</p> <p>The efficacy of JARDIANCE® Tablets according to patient baseline characteristics revealed no issues indicating an effect modifier.</p> <p>The interim analysis was not planned and conducted in this study.</p>		
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