Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Micatrio® Combination Tablets			
Name of active ingredient: Telmisartan / amlodipine / hydrochlorothiazide			
Report date: 20 February 2020	**Study number:** 1348.0006	**Version/Revision:** Ver. 1.0	**Version/Revision date:** Not applicable
Title of study:	The special drug use-results survey on long-term use of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed dose combination tablets in Patients with Hypertension		
Keywords:			
Rationale and background:	The Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices requires accumulating safety and effectiveness data of launched products in Japan for re-examination. The post marketing surveillance (PMS) plan is a part of the Japanese Risk Management Plan (J-RMP). The J-RMP is submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) as a part of Japanese Common Technical Document (J-CTD) and need to be approved by PMDA as approval condition. After the approval, the results of the PMS are required to be submitted to the Japanese regulatory authority, PMDA, as a part of the re-examination dossier.		
Research question and objectives:	This PMS was designed to investigate the safety, effectiveness and appropriate use of Micatrio® Combination Tablets in patients with hypertension under real-world use according to the Japanese package insert.		
Study design:	Non-interventional study based on newly collected data. The study consisted of a baseline visit and follow up visits at Weeks 4, 8, 12, 24, 36, and 52 for patients who had newly initiated Micatrio® Combination Tablets. The patients were followed up until discontinuation of Micatrio® Combination Tablets treatment or the end of study. All patients administrated Micatrio® Combination Tablets after the launch at the sites contracted with the sponsor were registered.		
Setting:	Number of sites: 95 sites Dosage: Micatrio® Combination Tablets, telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg Duration of observation: 52 weeks or until discontinuation of administration		

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	Registration period: February 2017 to January 2018 Study period: January 2017 to April 2019		
Subjects and study size, including dropouts:	Number of patients registered: 676 <u>Inclusion criteria</u> ・ Patients who were prescribed with Micatrio® Combination Tablets by the discretion of investigators based on the Japanese package insert ・ Patients who had never been treated with Micatrio® Combination Tablets before enrolment <u>Exclusion criteria</u> Patients who were participating/planned to participate in a clinical trial		
Variables and data sources:	**Variables:** Outcomes <u>Primary outcome (Safety set)</u> The frequency of patients with any suspected adverse drug reactions (ADRs) <u>Secondary outcome (Effectiveness set)</u> Effectiveness was assessed with a focus on the following variables as secondary outcomes. ・ Change from baseline in clinic diastolic blood pressure (DBP)[mmHg] at Week 52 ・ Change from baseline in clinic systolic blood pressure (SBP)[mmHg] at Week 52 <u>Further outcome (Safety set)</u> ・ Serious adverse events (AEs) ・ AEs for important identified risks ・ AEs for important potential risks ・ Relevant AEs <u>Further outcome (Effectiveness set)</u> Effectiveness was assessed with a focus on the following variables as further outcomes. ・ Change from baseline in clinic DBP and SBP[mmHg] at Week 8		

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	· Change from baseline in morning home DBP and SBP[mmHg] at Week 8 · Change from baseline in evening home DBP and SBP[mmHg] at Week 8 · Change from baseline in morning home DBP and SBP[mmHg] at Week 52 · Change from baseline in evening home DBP and SBP[mmHg] at Week 52 · The proportion of patients with clinic DBP <90 mmHg and clinic SBP <140 mmHg at Week 8 and Week 52 · The proportion of patients with clinic DBP <90 mmHg at Week 8 and Week 52 · The proportion of patients with clinic SBP <140 mmHg at Week 8 and Week 52 <u>Appropriate use of Micatrio® Combination Tablets</u> · Appropriately switching from active ingredients of Micatrio® Combination Tablets is defined as follows; - Treated with 3 active ingredients of Micatrio® Combination Tablets but treatment duration is less than 8 weeks, Not treated with 3 active ingredients of Micatrio® Combination Tablets but treatment duration is 8 weeks or more, Both 3 active ingredients of Micatrio® Combination Tablets and treatment duration were not appropriate, Unknown <u>Others</u> Demographics, Administration of Micatrio® Combination Tablets, Adherence, Previous/Concomitant medications, Controlled hypertension, Pulse rate, and Laboratory tests **Data sources:** Case report forms (CRFs) for individual patients were collected by electronic data capture (EDC) system.		
Statistical methods:	· The frequency and percentages of ADRs, SAEs, and other AEs will be		

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	tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics. · Descriptive statistics will be calculated for continuous secondary and further effectiveness outcomes. The frequency and percentages of categorical further effectiveness outcomes will be tabulated. · A mixed model repeated measures (MMRM) analysis was performed for change from baseline in clinic blood pressure at Week 52. · No interim analysis was performed in this trial.		
Results:	Patient disposition In this PMS, 676 patients were registered at 95 study sites in Japan. Case report forms were collected from 676 patients. Race and/or ethnicity data of patient was not collected. The safety set included 672 patients (99.41%) and the effectiveness set included 654 patients (96.75%). The number of dropouts (discontinued patients) was 118. Baseline patient characteristics In the safety set (N=672), more than half of the patients were male (403 patients, 59.97%) and aged ≥65 years old (463 patients, 68.90%). Mean age of patients (mean ± SD) was 68.8 ± 13.2 years (range, 17 to 97 years). Duration of hypertension (mean ± SD) was 7 ± 7 years in 338 patients with data on hypertension duration. Grade of renal function impairment was mild (285 patients, 42.41%) or moderate (205 patients, 30.51%). Most of the patients (518 patients, 77.08%) had concomitant disease. Primary outcome (Safety set) In the safety set (N=672), ADRs were reported in 32 patients (4.76%). The most frequently reported ADR (preferred term [PT]) was hypotension (7 patients, 1.04%), followed by blood pressure decreased (6 patients, 0.89%), renal impairment (3 patients, 0.45%), and hyperuricaemia, hyponatraemia, dizziness, and blood uric acid increased (2 patients each, 0.30%). Secondary outcome (Effectiveness set) At baseline, DBP and SBP (mean ± SD) were 75.1 ± 12.0 mmHg and		

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	135.3 ± 14.8 mmHg, respectively, and the changes from baseline were −2.0 ± 10.0 mmHg and −2.6 ± 15.4 mmHg, respectively, at Week 52. The least square (LS) mean of DBP and SBP (LS mean ± SE) were 75.0 ± 0.3 mmHg and 135.1 ± 0.5 mmHg at baseline, respectively, and the changes from baseline were −1.9 ± 0.4 mmHg and −2.6 ± 0.6 mmHg, respectively, at Week 52. <u>Further outcome (Safety set)</u> In the safety set (N=672), 72 patients were reported with any AEs (10.71%). In the safety set (N=672), at least one SAE was reported in 20 patients (2.98%). The most frequently affected SOCs were “Neoplasms benign, malignant and unspecified (incl cysts and polyps)”, “Metabolism and nutrition disorders”, “Nervous system disorders”, “Cardiac disorders”, and “Musculoskeletal and connective tissue disorders” (4 patients each, 0.60%), followed by “Gastrointestinal disorders” (3 patients, 0.45%). AEs defined as “important identified risks of Micatrio® Combination Tablets” in the Japanese RMP are Angioedema, Hyperkalaemia, Hyponatraemia, Renal dysfunction, Shock/syncope/unconsciousness, Hepatitis fulminant/hepatic dysfunction/jaundice, Hypoglycaemia, Anaphylaxis, Aplastic anaemia/haemolytic anaemia, Interstitial pneumonia/pulmonary oedema/respiratory distress including pneumonitis, Rhabdomyolysis, Agranulocytosis/leucopenia/thrombocytopenia, Atrioventricular block, Acute myopia/angle-closure glaucoma, Necrotising vasculitis, and Worsening of systemic lupus erythematosus. At least one ADR categorised into important identified risks defined above were reported in 7 patients (1.04%). The frequently reported ADRs (PT) were renal impairment (3 patients, 0.45%) and hyponatraemia (2 patients, 0.30%). AEs defined as “important potential risks of Micatrio® Combination Tablets” in the Japanese RMP is Malignancies. No ADR categorised into important potential risks was reported.		

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ADRs defined as "relevant ADR" are Hepatic function disorders, Renal function disorders, Diabetes, Hyperlipidemia, Hyperuricemia, and Hypotension.

At least one relevant ADR was reported in 21 patients (3.13%). The most frequently reported ADR (PT) was hypotension (7 patients, 1.04%), followed by blood pressure decreased (6 patients, 0.89%), renal impairment (3 patients, 0.45%), blood uric acid increased, hyperuricaemia, and dizziness (2 patients each, 0.30%).

The fatal cases were reported for 2 patients (0.30%) in the safety set (N=672). Patient [redacted] (aspiration, asphyxia, cardio-respiratory arrest, hypoxia, coma, and brain injury), patient [redacted] (acute myocardial infarction). The causal relationship between all of these events and Micatrio® Combination Tablets was assessed as not related by both of reporting physicians and the sponsor.

At least one serious adverse event (SAE) was reported in 20 patients (2.98%). The most frequently reported SAEs (PT) were dehydration and cerebral infarction (2 patients each, 0.30%).

Severe AEs were reported in 13 patients (1.93%).

Thirty two patients (4.76%) discontinued Micatrio® Combination treatment due to AEs. The most frequently reported AE leading to discontinuation (PT) was blood pressure decreased (5 patients, 0.74%), followed by dizziness and hypotension (4 patients each, 0.60%), renal impairment (3 patients, 0.45%), and dehydration and hyponatraemia (2 patients each, 0.30%).

At least one AE categorised into important identified risks was reported in 18 patients (2.68%). The most frequently reported AE (PT) categorised into important identified risks was hepatic function abnormal (5 patients, 0.74%), followed by hyponatraemia and renal impairment (3 patients each, 0.45%), and hyperkalaemia (2 patients, 0.30%).

At least one AE categorised into important potential risks (malignancies)

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was reported in 4 patients (0.60%). The reported AEs (PT) were bladder neoplasm, colon cancer, metastases to bone, pancreatic carcinoma, and brain neoplasm (patient each, 0.15%).

At least one relevant AE was reported in 35 patients (5.21%). The most frequently reported AEs (PT) were blood pressure decreased and hypotension (7 patients each, 1.04%), followed by hepatic function abnormal and dizziness (5 patients each, 0.74%), renal impairment and hyperuricaemia (3 patients each, 0.45%), diabetes mellitus, hyperglycaemia, and blood uric acid increased (2 patients each, 0.30%).

Further outcome (Effectiveness set)

・ Change from baseline in clinic DBP and SBP at Week 8

Clinic DBP and SBP (mean ± SD) were 75.0 ± 12.0 mmHg and 135.0 ± 14.9 mmHg at baseline, respectively, and the changes from baseline were −1.6 ± 9.4 mmHg and −3.1 ± 14.0 mmHg, respectively, at Week 8. The LS mean of DBP and SBP (LS mean ± SE) were 75.0 ± 0.3 mmHg and 135.1 ± 0.5 mmHg at baseline, respectively, and the changes from baseline were −1.4 ± 0.4 mmHg and −3.1 ± 0.6 mmHg, respectively, at Week 8.

・ Change from baseline in morning home DBP and SBP at Weeks 8 and 52

Morning home DBP and SBP (mean ± SD) were 77.1 ± 11.3 mmHg and 134.0 ± 14.2 mmHg at baseline, respectively. The changes in DBP and SBP (mean ± SD) from baseline were −3.2 ± 9.2 mmHg and −3.6 ± 12.0 mmHg at Week 8, and −2.5 ± 10.5 mmHg and −4.9 ± 15.0 mmHg at Week 52, respectively. The LS mean of morning home DBP and SBP (LS mean ± SE) were 76.8 ± 0.7 mmHg and 134.0 ± 1.0 mmHg at baseline, respectively. The changes in LS mean of DBP and SBP (LS mean ± SE) from baseline were −3.0 ± 0.8 mmHg and −4.5 ± 1.2 mmHg at Week 8, and −2.9 ± 0.9 mmHg and −5.1 ± 1.2 mmHg at Week 52, respectively.

・ Change from baseline in evening home DBP and SBP at Weeks 8 and 52

Evening home DBP and SBP (mean ± SD) were 71.7 ± 9.1 mmHg and 128.8 ± 14.4 mmHg at baseline, respectively. The changes in DBP and SBP (mean ± SD) from baseline were −0.9 ± 6.6 mmHg and −2.0 ±

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	12.7 mmHg at Week 8, and −0.5 ± 7.2 mmHg and −5.0 ± 12.3 mmHg at Week 52, respectively. The LS mean of evening home DBP and SBP (LS mean ± SE) were 71.2 ± 0.7 mmHg and 128.6 ± 1.1 mmHg at baseline, respectively. The changes in LS mean of DBP and SBP (LS mean ± SE) from baseline were −1.0 ± 0.9 mmHg and −2.8 ± 1.3 mmHg at Week 8, and −0.6 ± 0.9 mmHg and −5.1 ± 1.4 mmHg at Week 52, respectively. ・ The proportion of patients with clinic DBP <90 mmHg and SBP <140 mmHg at Weeks 8 and 52 The proportion of patients with clinic DBP <90 mmHg and SBP <140 mmHg was 67.64% (441/652 patients) at baseline, 73.50% (344/468) at Week 8, and 74.46% (376/505) at Week 52. ・ The proportion of patients with clinic DBP <90 mmHg at Weeks 8 and 52 The proportion of patients with clinic DBP <90 mmHg was 91.26% (595/652 patients) at baseline, 91.67% (429/468) at Week 8, and 93.27% (471/505) at Week 52. ・ The proportion of patients with clinic SBP <140 mmHg at Week 8 and Week 52. The proportion of patients with clinic SBP <140 mmHg was 69.57% (455/654 patients) at baseline, 75.16% (354/471 patients) at Week 8, and 76.09% (385/506 patients) at Week 52. <u>Appropriate use of Micatrio® Combination Tablets</u> The majority of patients (643 patients, 95.68%) used Micatrio® Combination Tablets appropriately. Inappropriate use based on Japanese package insert were reported in 29 patients (4.32%).		

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Discussion:	Adverse Drug Reactions The overall incidence of ADRs reported during the course of this PMS (4.76% [32/672 patients]) was lower than that described in the Japanese package insert of Micatrio® Combination Tablets (14.4% [40/278]). Most ADRs reported in the PMS were the same as those listed in the Japanese package insert of Micatrio® Combination Tablets, suggesting no remarkable changes were found on the safety profiles from the time of Micatrio® Combination Tablets approval on 28 September 2016. Effectiveness (Change from baseline in clinic DBP and SBP)[mmHg] at Week 52) No remarkable change was found in clinic DBP and SBP at Week 52, indicating that patients' blood pressures were well controlled and maintained. From the results for change in blood pressure at Week 52, consistent effectiveness profile was found for long-term use of Micatrio® Combination Tablets as same as the results which were obtained from clinical trials at the time of Micatrio® Combination Tablets approval on 28 September 2016. No remarkable change was noted in DBP and SBP at each time point, as well as proportion of patients with clinic DBP <90 mmHg and/or SBP <140 mmHg, indicating that patients' blood pressures were well controlled and maintained. Appropriate use of Micatrio® Combination Tablets The majority of patients (490 patients, 97.03%) used Micatrio® Combination Tablets appropriately. In conclusion, the PMS results raised no new concerns on the safety and effectiveness profile, and appropriate use of Micatrio® Combination Tablets in long-term daily use in Japanese patients with hypertension.		
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Names and	[redacted]		

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