Study Results Summary for Public Disclosure

Study title	Special drug use surveillance of Entresto Tablets (Hypertension, CLCZ696A1402, ENLIGHT)
Date	14-Apr-2026
NIS type	NIS with Primary Data Collection; Novartis Drug NIS
Keywords	Japan, sacubitril valsartan sodium hydrate, hypertension, non-interventional study, post-marketing surveillance
Rationale and background	It was determined to conduct this study to collect information on the safety specifications under the actual clinical practice of Entresto (sacubitril valsartan sodium hydrate) in patients with hypertension in Japan to confirm the occurrence and timing of onset of events related to the safety specifications and investigate risk factors. Since the observation period of this study was set at 1 year (52 weeks), which is a long period, the study will be conducted as a special drug use surveillance.
Study objectives	To evaluate the safety and effectiveness of Entresto Tablets during the first 52 weeks of treatment in patients with hypertension in a real-world setting.
Study design	This is a multicenter observational study with a central registration system without a control group.
Study requirements	Not applicable
Study population	Inclusion criteria 1. Patients who have given written consent to participate in this study before the start of treatment with Entresto 2. Patients who used Entresto for the first time for the indication of hypertension Exclusion criteria 1. Patients who have received a formulation containing the same ingredient as Entresto (including investigational product or post-marketing clinical study drug) 2. The following patients for whom administration of Entresto is contraindicated in the package insert: • Patients with a history of hypersensitivity to any of the ingredients of Entresto • Patients who are receiving angiotensin-converting enzyme inhibitors (alacepril, imidapril hydrochloride, enalapril maleate, captopril, quinapril hydrochloride, cilazapril hydrate, temocapril hydrochloride, delapril hydrochloride, trandolapril, benazepril hydrochloride, perindopril erbumine, and lisinopril hydrate) or who discontinued these drugs within 36 hours. • Patients with a history of angioedema (angioedema due to angiotensin II receptor antagonists or angiotensin converting

	enzyme inhibitors, hereditary angioedema, acquired angioedema, idiopathic angioedema, etc.) • Patients with diabetes mellitus who are receiving aliskiren fumarate • Patients with severe hepatic impairment (Child-Pugh class C) • Pregnant or possibly pregnant women 3. Patients with a history or complication of cardiac failure 4. Patients who have been hospitalized at the start of treatment with Entresto
Investigation items	Patient characteristics, administration status of Entresto, discontinuation of the study, concomitant medications, vital signs, laboratory tests, pregnancy status (only for women), adverse events, and autopsy status (only for patients who died)
Results	[Study overview] The study results are shown based on the data obtained between the start of the study (01-Jul-2023) and the end of the study (04-Nov-2025). In this study, 1125 participants were registered from 118 sites. [Patient composition] The safety analysis population consisted of 1124 patients after excluding 1 patient with "violation of inclusion/exclusion criteria in the protocol" from the 1125 patients with locked case report forms. The effectiveness analysis population consisted of 1096 patients after excluding 28 patients with “effectiveness evaluation not performed/not specified” from the 1124 patients in the safety analysis population. [Patient characteristics] The percentage of male participants was 57.7% (649 of 1124 patients). The mean ± SD age at the start of treatment with Entresto was 69.3 ± 13.56 years and the median (minimum to maximum) was 72.0 (28-99) years. Patients aged < 75 years accounted for 57.7% (648/1124 patients) and late elderly patients aged ≥ 75 years accounted for 42.3% (476/1124 patients). Mean ± SD of sitting systolic blood pressure (sSBP) at the start of treatment with Entresto was 147.6 ± 19.35 mmHg (n = 1079) and sitting diastolic blood pressure (sDBP) was 82.4 ± 14.37 mmHg (number of patients: 1062). Category of blood pressure at the start of treatment with Entresto was Grade I in 39.3% (442/1124 patients), Grade II/III in 26.7% (300/1124 patients), others (other than Grade I to III) in 28.7% (323/1124 patients), and unknown/not specified in 5.2% (59/1124 patients). The percentage of patients with cardiac disease as complication was 29.3% (329/1124 patients), while renal impairment was 22.4% (252/1124 patients), hepatic impairment was 10.1% (114/1124 patients), cerebrovascular disorder was 9.0% (101/1124 patients), diabetes mellitus was 26.2% (295/1124 patients), and dyslipidemia was 53.1% (597/1124 patients). The percentage of patients who used antihypertensive drugs in the past was 94.0% (1056/1124 patients), and Entresto was not used as the first-line drug for the treatment of hypertension in many of the patients.

	[Administration status of Entresto] Duration of treatment with Entresto (including treatment interruption) was ≥ 52 weeks in 85.2% (958/1124) of patients. The dose of Entresto was changed in 16.5% (185/1124 patients) including "dose increase only" in 10.6% (119/1124 patients), "dose reduction only" in 3.3% (37/1124 patients), and "dose increase and dose reduction" in 2.6% (29/1124 patients). The most common daily dose of Entresto at each visit was 200 mg in 79.9% (898/1124 patients) at the start of treatment with Entresto. The percentage of patients receiving 200 mg was also highest at Week 52 and was 73.7% (707/959 patients). In this study, many patients started treatment at 200 mg and maintained the dose. The dose was increased to 400 mg as needed. [Safety] The incidence of adverse events was 12.1% (136/1124 patients). Common adverse events (≥ 1.0% of patients) by preferred term (PT) were hypertension in 1.5% (17/1124 patients), blood pressure decreased in 1.3% (15/1124 patients), hypotension in 1.2% (13/1124 patients), and dizziness in 1.1% (12/1124 patients). The incidence of serious adverse events was 3.1% (35/1124 patients). The incidence of adverse drug reactions was 5.4% (61/1124 patients). Common adverse drug reactions by PT (reported in ≥ 2 patients) were hypotension and blood pressure decreased in 1.2% (13/1124 patients) each, dizziness in 1.1% (12/1124 patients), hyperkalaemia in 0.6% (7/1124 patients), and hypokalaemia, hypertension, nausea, pollakiuria, feeling abnormal, and malaise in 0.2% (2/1124 patients) each. All other events occurred in 1 patient each. Regarding the occurrence of adverse drug reactions by time of initial onset, the incidence tended to be higher during the period from Day 1 to Month 1, which was the early stage of treatment with Entresto. By PT, dizziness tended to occur more frequently in the early stage of administration. The incidence of serious adverse drug reactions was 0.3% (3/1124 patients). The incidence of adverse drug reactions that led to treatment discontinuation was 2.7% (30/1124 patients). Common adverse drug reactions that led to treatment discontinuation by PT (reported in ≥ 2 patients) were dizziness in 0.7% (8/1124 patients), blood pressure decreased in 0.6% (7/1124 patients), hypotension in 0.5% (6/1124 patients), and nausea and malaise in 0.2% (2/1124 patients) each. A total of 7 adverse events leading to death occurred in 6 patients. None of these events were considered related to Entresto. Regarding safety specifications, the incidence of adverse events related to hypotension was 3.0% (34/1124 patients), the incidence of adverse events related to hyperkalemia was 0.6% (7/1124 patients), and the incidence of adverse events related to renal impairment/failure was 1.0% (11/1124 patients), showing that the incidence of adverse events related to hypotension was the highest. The incidences of all events were low in this study, and there was no tendency for the incidences of the safety specifications to increase markedly.

	Odds ratios (OR) for the risk factors in the safety specifications, which were secondary endpoints of this study, were examined using a multivariate logistic regression model. As a result, a factor with a lower limit of 95% confidence interval (CI) of adjusted OR exceeded 1 among adverse events related to hypotension was specific complication: cardiac disease (adjusted OR for "present" versus "absent", 2.94; 95% CI, 1.39, 6.22). A factor with a lower limit of 95% CI of adjusted OR exceeded 1 among adverse events related to hyperkalemia were specific complications: renal impairment (adjusted OR for "present" versus "absent", 4.92; 95% CI, 1.02, 23.82) and concomitant medication: diuretics (at the start of treatment with Entresto) (adjusted OR for "present" versus "absent", 8.65; 95% CI, 1.46, 51.34). However, the results should be interpreted with caution due to the limited number of patients with concomitant use of diuretics. Risk factors for adverse events related to renal impairment/failure could not be identified since only 2 patients were reported to have such events. Use in children or pregnant women was not reported. There were no clear concerns regarding safety in the late elderly patients (≥ 75 years) and patients with hepatic impairment. In patients with renal impairment, the incidence of adverse drug reactions by severity of renal impairment was 5.8% (9/155 patients) in patients with mild renal impairment, 3.6% (3/83 patients) in patients with moderate renal impairment, and 14.3% (2/14 patients) in patients with severe renal impairment, showing a higher incidence in patients with severe renal impairment than 5.4% (47/872 patients) in patients without renal impairment. However, the results should be interpreted with caution due to the limited number of patients with renal impairment. [Effectiveness] Using the linear mixed effect model, the change (least squares mean) in sSBP was -13.2 mmHg (95% CI: -14.2, -12.1) at 8 weeks, -16.8 mmHg (95% CI: -17.9, -15.7) at 24 weeks, and -17.0 mmHg (95% CI: -18.1, -15.8) at 52 weeks of treatment with Entresto. For sDBP, this was -5.5 mmHg (95% CI: -6.2, -4.8) at 8 weeks, -7.5 mmHg (95% CI: -8.2, -6.8) at 24 weeks, and -8.0 mmHg (95% CI: -8.8, -7.3) at 52 weeks of treatment with Entresto. Both sSBP and sDBP decreased over time from the start of treatment with Entresto until around Week 24 then maintained thereafter until Week 52 without marked changes. The percentage of patients who achieved blood pressure control (reference value according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2019 [JSH2019]) was 28.5% (307/1076 patients) at Week 8, 55.0% (309/562 patients) at Week 52, and 52.6% (576/1095 patients) at the final evaluation point. The percentage of patients who achieved improvement in sSBP (reference value according to JSH2019) was 39.9% (429/1076 patients) at Week 8, 69.8% (392/562 patients) at Week 52, and 69.8% (765/1096 patients) at the final evaluation point. The percentage of patients who achieved improvement in sDBP (reference value according to JSH2019) was 48.3% (520/1076 patients) at Week 8, 79.9% (445/557 patients) at Week 52, and 80.2% (874/1090 patients) at the final evaluation point.
Conclusion	The safety results of this study did not show any tendencies that are different from the known safety profile of Entresto, and no particular concern was

	identified. Therefore, no additional measure was considered necessary based on the results of this study. In addition, the results also demonstrated the effectiveness of Entresto in actual clinical settings to a certain extent. Safety information will continue to be collected through routine pharmacovigilance activities described in the risk management plan of Entresto, and appropriate measures will be taken if any new safety concern is identified.

List of abbreviations

Abbreviation	Unabbreviated term (English)
CI	Confidence Interval
JSH	The Japanese Society of Hypertension
NIS	Non-interventional Study
OR	Odds Ratio
PT	Preferred Term
sDBP	sitting Diastolic Blood Pressure
sSBP	sitting Systolic Blood Pressure