This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix

Summary of Disproportionality Analysis Using VigiBase

September 9, 2025

Purpose of investigation	Angioedema is included as an adverse drug reaction in the package inserts of angiotensin-converting enzyme inhibitors (hereinafter referred to as “ACE inhibitors”), angiotensin II receptor blockers (hereinafter referred to as “ARBs”), angiotensin receptor neprilysin inhibitor, and direct renin inhibitor (hereinafter collectively referred to as “renin angiotensin system inhibitors”). Taking into account that language regarding intestinal angioedema is included for some of the ACE inhibitors, the necessity of taking safety measures regarding intestinal angioedema for all the renin angiotensin system inhibitors was evaluated.
Scope of investigation	Target drugs • Drugs categorized as "C09A ACE INHIBITORS, PLAIN (ATC3)" or "C09C Angiotensin II receptor blockers (ARBs), plain (ATC3)" under the ATC classification; "Sacubitril; Valsartan (Active ingredient)," "Aliskiren (Active ingredient)" Target events • MedDRA v28.0 PT "Intestinal angioedema"
Outline of method	A disproportionality analysis*2 for reports of intestinal angioedema associated with renin angiotensin system inhibitors was performed using the dataset of the World Health Organization (WHO) Individual Case Safety Reports (ICSRs) Global Database (VigiBase)*1 as of July 1, 2025. Information components (ICs) were calculated as signal indices, and when the lower limit of the 95% confidence interval (IC_{025}) was greater than 0, it was considered that a signal was detected (Eur J Clin Pharmacol. 1998; 54: 315–21, Pharmacoepidemiol Drug Saf. 2009; 18: 427-36). VigiLyze, a signal detection/management tool of the WHO, was used for the data analysis.
Outline of results	Results The results of the disproportionality analysis for reports of intestinal angioedema associated with renin-angiotensin system inhibitors using

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

VigiBase are shown in Table 1.

The number of adverse reactions of "intestinal angioedema" reported for several ACE inhibitors (lisinopril, enalapril, ramipril, perindopril, and benazepril) and ARBs (losartan, olmesartan, irbesartan, and valsartan) was shown to be statistically higher than would be expected based on the entire database.

Table 1: IC values for "intestinal angioedema" in the VigiBase Dataset

Active ingredient Note 1)	Number of adverse drug reaction reports (observed)	Number of reports of intestinal angioedema (observed)	Number of reports of intestinal angioedema (expected)	IC	IC_{025}
Lisinopril	66,785	250	1	7.5	7.4
Losartan	39,273	28	0	4.8	4.3
Enalapril	81,444	25	1	4.1	3.4
Ramipril Note2)	41,478	14	1	3.8	3.0
Perindopril	37,900	13	0	3.8	2.9
Olmesartan	18,253	6	0	3.2	1.8
Irbesartan	17,931	5	0	2.9	1.4
Benazepril	4,114	4	0	3.0	1.3
Valsartan	39,915	5	1	2.5	0.9
Captopril	33,350	3	0	1.9	-0.1
ARB	33	1	0	1.6	-2.2
Sacubitril valsartan	121,629	2	2	0.3	-2.3
Quinapril Note 2)	6,224	1	0	1.4	-2.4

Note 1) The number of cases of intestinal angioedema for all drugs was 414.
Note 2) Not marketed in Japan.

Discussion based on the results

The results of the disproportionality analysis using VigiBase suggested a relationship between some renin-angiotensin system inhibitors and intestinal angioedema*3. It was determined that the results of the disproportionality analysis be regarded as one of the bases for the revisions to additionally include intestinal angioedema in the package inserts of renin-angiotensin system inhibitors.

*1: Data from VigiBase, the WHO global database of reported adverse events of medicinal products, were used for this analysis. Causal relationships between the event and a medicine may be difficult to establish due to limitations in the data.

*2: The disproportionality analysis is a hypothesis generating or refinement approach.

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

*3: The information and any results and conclusions drawn do not represent the opinions of Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring, or of the World Health Organization.