独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

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Summary of Investigation Results

Angiotensin-converting enzyme inhibitors
Preparations containing angiotensin II receptor blocker
Angiotensin receptor-neprilysin inhibitor
Direct renin inhibitor

September 9, 2025

Non-proprietary name

See attachment.

Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

A cautionary statement regarding intestinal angioedema should be added to “angioedema” in the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

Investigation results and background of the revision

Cases reported in Japan and overseas and the results of a disproportionality analysis using the WHO Individual Case Safety Reports (ICSRs) Global Database (VigiBase)*[1] were evaluated for intestinal angioedema associated with angiotensin-converting enzyme

inhibitors, angiotensin II receptor blockers, angiotensin receptor-neprilysin inhibitor, and direct renin inhibitor (hereinafter collectively referred to as “RAS inhibitors”). As a result of consultation with expert advisors, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary for the RAS inhibitors for which no precautions are included in the current electronic package insert, taking into consideration the following:

- For RAS inhibitors, angioedema itself is included in the 11.1 Clinically Significant Adverse Reactions section, and it is an identified risk. Accordingly, intestinal angioedema, a type of angioedema, may be considered to be a potential risk.
- For some drug products, no cases involving intestinal angioedema have been reported as adverse reactions in Japan or overseas. However, for multiple drug products, cases in which a causal relationship between intestinal angioedema and the drug products was reasonably possible have been identified.
- A disproportionality analysis performed by the PMDA using VigiBase showed statistically higher numbers of reported adverse reactions involving intestinal angioedema for multiple angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers than would be expected based on the entire database*2. (See appendix.)

Reference: Number of cases*3,*4 and patient mortalities involving intestinal angioedema reported in Japan and overseas

•Cases reported in Japan

1. to 4., 6., 7., 12., 27.

No cases have been reported to date.

5.

One case has been reported to date. (A causal relationship between the drug and the event was reasonably possible for this case.)

No patient mortalities have been reported to date.

8.

A total of 2 cases have been reported to date. (A causal relationship between the drug and the event could not be established for any of these cases.)

No patient mortalities have been reported to date.

9.

One case has been reported to date. (A causal relationship between the drug and the event could not be established for this case.)

No patient mortalities have been reported to date.

10.
One case has been reported to date. (A causal relationship between the drug and the event was reasonably possible for this case.)
No patient mortalities have been reported to date.
11.
A total of 3 cases have been reported to date (including 2 cases in which a causal relationship between the drug and the event was reasonably possible).
No patient mortalities have been reported to date.
26.
A total of 2 cases have been reported to date (including 1 case in which a causal relationship between the drug and the event was reasonably possible).
No patient mortalities have been reported to date.

•Cases reported overseas
1. to 4., 6., 10.
No cases have been reported to date.
5.
A total of 14 cases have been reported to date (including 11 cases in which a causal relationship between the drug and the event was reasonably possible).
One instance of patient mortality has been reported to date. (A causal relationship between the drug and the death following the event could not be established for this case.)
7.
One case has been reported to date. (A causal relationship between the drug and the event was reasonably possible for this case.)
No patient mortalities have been reported to date.
8.
A total of 3 cases have been reported to date. (A causal relationship between the drug and the event could not be established for any of these cases.)
No patient mortalities have been reported to date.
9.
One case has been reported to date. (A causal relationship between the drug and the event could not be established for this case.)
No patient mortalities have been reported to date.

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11.
A total of 2 cases have been reported to date (including 1 case in which a causal relationship between the drug and the event was reasonably possible).
No patient mortalities have been reported to date.
12.
A total of 7 cases have been reported to date (including 5 cases in which a causal relationship between the drug and the event was reasonably possible).
No patient mortalities have been reported to date.
26.
A total of 3 cases have been reported to date. (A causal relationship between the drug and the event could not be established for any of these cases.)
No patient mortalities have been reported to date.
27.
One case has been reported to date. (A causal relationship between the drug and the event could not be established for this case.)
No patient mortalities have been reported to date.

*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 information, 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.
*3 Among the cases collected in the PMDA's safety database for drugs, those meeting the following conditions were retrieved:
a) Cases that fell under MedDRA v28.0 PT “intestinal angioedema” or “gastrointestinal oedema” were retrieved.
b) Among the cases that fell under “angioedema” in MedDRA v28.0 PT, those with symptoms such as abdominal pain and diarrhoea that may be related to intestinal angioedema were retrieved.
c) Among the cases that fell under a) or b) above, cases for which the outcomes of the related events could not be identified from the information in the column of outcomes or clinical courses were excluded.

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*4 Causality assessment of the cases was performed for drug products containing a single active ingredient.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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Attachment

Angiotensin-converting enzyme inhibitors (drug preparations for which no precautions regarding intestinal angioedema are included in the 11.1 Clinically Significant Adverse Reactions section)

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
1	Alacepril	Cetapril Tablets 25 mg, and the others	Sumitomo Pharma Co., Ltd. and the others	June 1988	Essential hypertension, renal hypertension
2	Imidapril hydrochloride	Tanatril Tablets 2.5, 5, 10, and the others	Mitsubishi Tanabe Pharma Corporation and the others	December 1993	[Tablets 2.5, 5] ・Hypertension •Renal parenchymal hypertension •Diabetic nephropathy associated with type 1 diabetes mellitus [Tablets 10] •Hypertension •Renal parenchymal hypertension
3	Delapril hydrochloride	Adecut 7.5 mg, 15 mg, 30 mg Tablets	T's Seiyaku Co., Ltd.	April 1989	Essential hypertension, renal hypertension, renovascular hypertension
4	Trandolapril	Odric Tablets 0.5 mg, 1 mg, and the others	Nippon Shinyaku Co., Ltd. and the others	May 1996	Hypertension
5	Perindopril erbumine	Coversyl Tablets 2 mg, 4 mg, and the others	Kyowa Kirin Co., Ltd. and the others	April 1998	Hypertension

Preparations containing angiotensin II receptor blocker

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
6	Azilsartan	Azilva Tablets 10 mg, 20 mg, 40 mg, Azilva Granules 1%, and the others	Takeda Pharmaceutical	[Tablets 20, 40] May 2012 [Tablets 10]	Hypertension

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
			Company Limited. and the others	June 2014 [Granules] December 2021	
7	Irbesartan	Avapro Tablets 50 mg, 100 mg, 200 mg, and the others	Sumitomo Pharma Co., Ltd. and the others	[Tablets 50, 100] July 2008 [Tablets 200] June 2013	Hypertension
		Irbetan Tablets 50 mg, 100 mg, 200 mg, and the others	Shionogi Pharma Co., Ltd. and the others		
8	Olmesartan medoxomil	Olmetec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg, and the others	Daiichi Sankyo Co., Ltd. and the others	[OD Tablets 10, 20, 40] December 2015 [OD Tablets 5] June 2017	Hypertension
9	Candesartan cilexetil	Blopress Tablets 2, 4, 8, 12, and the others	T's Seiyaku Co., Ltd. and the others	June 1999	[Tablets 2, 4, 8, 12] Hypertension Renal parenchymal hypertension [Tablets 2, 4, 8] Patients with the following disease to whom administration of angiotensin-converting enzyme inhibitors is not appropriate: Chronic cardiac failure (mild to moderate cases)
10	Telmisartan	Micardis Tablets 20 mg, 40 mg, 80 mg, and the others	Boehringer Ingelheim Japan, Inc. and the others	[Tablets 20, 40] January 2005 [Tablets 80] October 2010	Hypertension
11	Valsartan	Diovan Tablets 20 mg, 40 mg, 80 mg, 160 mg, Diovan OD Tablets 20 mg,	Novartis Pharma K.K. and the others	[Tablets 20, 40, 80] November 2000 [Tablets 160] December 2004	Hypertension

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
		40 mg, 80 mg, 160 mg, and the others		[OD Tablets] July 2013	
12	Losartan potassium	Nu-Lotan Tablets 25 mg, 50 mg, 100 mg, and the others	Organon K.K. and the others	[Tablets 25, 50] August 1998 [Tablets 100] March 2009	•Hypertension •Diabetic nephropathy in type 2 diabetes mellitus accompanied by hypertension and proteinuria
13	Azilsartan/ amlodipine besilate	Zacras Combination Tablets LD, HD, and the others	Takeda Pharmaceutical Company Limited. and the others	June 2014	Hypertension
14	Irbesartan/ amlodipine besilate	Aimix Combination Tablets LD, HD, and the others	Sumitomo Pharma Co., Ltd. and the others	December 2012	Hypertension
15	Irbesartan/ trichlormethiazide	Irtra Combination Tablets LD, HD	Shionogi Pharma Co., Ltd.	September 2013	Hypertension
16	Olmesartan medoxomil/ azelnidipine	Rezaltas Combination Tablets LD, HD	Daiichi Sankyo Co., Ltd.	April 2010	Hypertension
17	Candesartan cilexetil/ amlodipine besilate	Unisia Combination Tablets LD, HD, and the others	T's Seiyaku Co., Ltd. and the others	June 2010	Hypertension
18	Candesartan cilexetil/ hydrochlorothiazide	Ecard Combination Tablets LD, HD, and the others	T's Seiyaku Co., Ltd. and the others	March 2009	Hypertension
19	Telmisartan/ amlodipine besilate	Micamlo Combination Tablets AP, BP, and the others	Boehringer Ingelheim Japan, Inc. and the others	[Combination Tablets AP] October 2010 [Combination Tablets BP] May 2013	Hypertension

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
20	Telmisartan/ amlodipine besilate/ hydrochlorothiazide	Micatrio Combination Tablets	Boehringer Ingelheim Japan, Inc.	November 2016	Hypertension
21	Telmisartan/ hydrochlorothiazide	Micombi Combination Tablets AP, BP, and the others	Boehringer Ingelheim Japan, Inc. and the others	June 2009	Hypertension
22	Valsartan/ amlodipine besilate	Exforge Combination OD Tablets, Exforge Combination Tablets, and the others	Novartis Pharma K.K. and the others	[Combination Tablets] April 2010 [Combination OD Tablets] June 2015	Hypertension
23	Valsartan/cilnidipine	Atedio Combination Tablets	EA Pharma Co., Ltd.	May 2014	Hypertension
24	Valsartan/ hydrochlorothiazide	Co-Dio Combination Tablets MD, EX, and the others	Novartis Pharma K.K. and the others	March 2009	Hypertension
25	Losartan potassium/ hydrochlorothiazide	Preminent Tablets LD, HD, and the others	Organon K.K. and the others	[Combination Tablets LD] December 2006 [Combination Tablets HD] April 2014	Hypertension

Angiotensin receptor-neprilysin inhibitor

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
26	Sacubitril valsartan sodium hydrate	Entresto Tablets 50 mg, 100 mg, 200 mg, Entresto Granules for Pediatric 12.5 mg, 31.25 mg	Novartis Pharma K.K.	[Tablets] August 2020 [Granules for Pediatric] May 2024	[Tablets 50, 100, 200] Adults Chronic cardiac failure The use is limited to patients receiving standard treatment of chronic heart failure. Children

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
					Chronic cardiac failure [Tablets 100, 200] Hypertension [Granules for Pediatric] Chronic cardiac failure

Direct renin inhibitor

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
27	Aliskiren fumarate	Rasilez Tablets 150 mg	OrphanPacific, Inc.	October 2009	Hypertension