



Summary of Investigation Results

Angiotensin-converting enzyme inhibitors Preparations containing angiotensin II receptor blocker

Angiotensin receptor-neprilysin inhibitor Direct renin inhibitor

May 9, 2023

Non-proprietary name

See attachment.

Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

- Angiotensin-converting enzyme inhibitors, preparations containing angiotensin II receptor blocker, direct renin inhibitor

<New instructions>

The 9.4 Patients with Reproductive Potential section should be newly added, and a statement that this drug should be administered to women of child-bearing potential only if the potential therapeutic benefits are considered to outweigh the potential risks and precautions for cases where administration to women of child-bearing potential is necessary should be added.

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<Old instructions>

In the Use in Pregnant, Parturient and Nursing Women section, a statement that this drug should be administered to women of child-bearing potential only if the potential therapeutic benefits are considered to outweigh the potential risks and precautions for cases where administration to women of child-bearing potential is necessary should be added.

- Sacubitril valsartan sodium hydrate

In the 9.4 Patients with Reproductive Potential section, a statement that this drug should be administered to women of child-bearing potential only if the potential therapeutic benefits are considered to outweigh the potential risks and precautions for cases where administration to women of child-bearing potential is necessary should be added.

Investigation results and background of the revision

Reported cases (cases involving adverse drug reactions in fetuses and neonates) in which adverse foetal and neonatal outcomes are suspected to be due to exposure to the target drugs investigated during pregnancy were evaluated. Several cases involving adverse drug reactions in fetuses and neonates due to exposure to the target drugs during pregnancy have been reported. Among them, pregnancies had not been recognized by healthcare professionals or the pregnant women in some cases, which resulted in exposure to the target drugs in those women. As a result of consultation with expert advisors on the necessity of revision of Precautions, taking into account the reported cases for which adverse foetal and neonatal outcomes are suspected to be due to exposure to the target drugs during pregnancy, the MHLW/PMDA concluded that revision of Precautions was necessary since additional precautions for the use in women of child-bearing potential are necessary in view of the cases intermittently reported despite the fact that the precautionary statement that these drugs should not be administered to pregnant women is already included in the package inserts.

Reference: Number of cases* and patient mortalities involving adverse reactions in fetuses and neonates due to exposure during pregnancy reported† in Japan

Angiotensin-converting enzyme inhibitors

One case has been reported to date.

No patient mortalities have been reported to date.

1. Alacepril



- No cases have been reported to date.
- 2. Imidapril hydrochloride
No cases have been reported to date.
- 3. Enalapril maleate
One case has been reported to date.
No patient mortalities have been reported to date.
- 4. Captopril
No cases have been reported to date.
- 5. Temocapril hydrochloride
No cases have been reported to date.
- 6. Delapril hydrochloride
No cases have been reported to date.
- 7. Trandolapril
No cases have been reported to date.
- 8. Benazepril hydrochloride
No cases have been reported to date.
- 9. Perindopril erbumine
No cases have been reported to date.
- 10. Lisinopril hydrate
No cases have been reported to date.

Preparations containing angiotensin II receptor blocker

A total of 23 cases have been reported to date (including 1 case in which 2 different preparations containing angiotensin II receptor blocker were administered).

A total of 7 patient mortalities have been reported to date.

- 11. Azilsartan
One case has been reported to date.
No patient mortalities have been reported to date.
- 12. Irbesartan
No cases have been reported to date.
- 13. Olmesartan medoxomil



A total of 6 cases have been reported to date.

A total of 4 patient mortalities have been reported to date.

14. Candesartan cilexetil

A total of 6 cases have been reported to date.

A total of 2 patient mortalities have been reported to date.

15. Telmisartan

A total of 2 cases have been reported to date.

No patient mortalities have been reported to date.

16. Valsartan

A total of 3 cases have been reported to date.

No patient mortalities have been reported to date.

17. Losartan potassium

A total of 3 cases have been reported to date.

No patient mortalities have been reported to date.

18. Azilsartan/amlodipine besilate

No cases have been reported to date.

19. Irbesartan/amlodipine besilate

No cases have been reported to date.

20. Irbesartan/trichlormethiazide

No cases have been reported to date.

21. Olmesartan medoxomil/azelnidipine

One case has been reported to date.

No patient mortalities have been reported to date.

22. Candesartan cilexetil/amlodipine besilate

No cases have been reported to date.

23. Candesartan cilexetil/hydrochlorothiazide

No cases have been reported to date.

24. Telmisartan/amlodipine besilate

No cases have been reported to date.

25. Telmisartan/amlodipine besilate/hydrochlorothiazide

No cases have been reported to date.



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26. Telmisartan/hydrochlorothiazide

No cases have been reported to date.

27. Valsartan/amlodipine besilate

One case has been reported to date.

One instance of patient mortality has been reported to date.

28. Valsartan/cilnidipine

No cases have been reported to date.

29. Valsartan/hydrochlorothiazide

One case has been reported to date.

No patient mortalities have been reported to date.

30. Losartan potassium/hydrochlorothiazide

No cases have been reported to date.

Angiotensin receptor-neprilysin inhibitor

31. Sacubitril valsartan sodium hydrate

No cases have been reported to date.

Direct renin inhibitor

32. Aliskiren fumarate

No cases have been reported to date.

*: Among cases collected in the PMDA's database for adverse drug reactions, etc. report, those retrieved by the following conditions

- Retrieved by MedDRA ver.25.1 SMQ "pregnancy and neonatal topics," data lock (January 31, 2023)
- Cases reported after 2014 when PMDA Alert for Proper Use of Drugs (September 2014) "Adverse Events in Pregnant Women and Foetuses Associated With Use of Angiotensin II Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors" was issued.
- Cases in which the route of administration was "transplacental"
- Cases in which it was obvious that exposure to the target drugs occurred before pregnancy based on the column of clinical course were excluded.

Of note, the possibility of a causal relationship between the drugs and events was not evaluated.

†: Among cases involving adverse drug reactions in foetuses and neonates due to exposure to the drugs during pregnancy, the cases for which it was stated that pregnancies had not been recognized by the pregnant women in the column of clinical course, etc. of the case report form of adverse drug reactions



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were as follows: No case out of one case for angiotensin-converting enzyme inhibitors; eleven cases out of 23 cases for preparations containing angiotensin II receptor blocker.

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

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	Enalapril maleate	Renivace Tablets 2.5, 5, 10, and the others	Organon K.K., and the others	July 1986	Essential hypertension, renal hypertension, renovascular hypertension, malignant hypertension Patients with the following disease who do not sufficiently respond to basic treatment with digitalis preparations, diuretics, etc.: Chronic cardiac failure (mild to moderate cases)
4	Captopril	Captopril Tablets 12.5 mg, 25 mg, Captopril Fine Granules 5%, and the others	Alfresa Pharma Corporation, and the others	<Captopril Tablets 12.5 mg, 25 mg, Captopril Fine Granules 5%> February 1983	<Tablets 12.5 mg, 25 mg, Fine Granules 5%> Essential hypertension, renal hypertension, renovascular hypertension, malignant hypertension



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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
		Captoril-R Capsules 18.75 mg		<Captoril-R Capsules 18.75 mg> February 1989	<R Capsules 18.75 mg> Essential hypertension, renal hypertension
5	Temocapril hydrochloride	Acecol Tablets 1 mg, 2 mg, 4 mg, and the others	Alfresa Pharma Corporation, and the others	August 1994	Hypertension, renal parenchymal hypertension, renovascular hypertension
6	Delapril hydrochloride	Adecut 7.5 mg, 15 mg, 30 mg Tablets	Teva Takeda Pharma Ltd.	April 1989	Essential hypertension, renal hypertension, renovascular hypertension
7	Trandolapril	Odric Tablets 0.5 mg, 1 mg, and the others	Nippon Shinyaku Co., Ltd., and the others	May 1996	Hypertension
8	Benazepril hydrochloride	Cibacen Tablets 2.5 mg, 5 mg, 10 mg, and the others	Sun Pharma Japan Limited., and the others	April 1993	Hypertension
9	Perindopril erbumine	Coversyl Tablets 2 mg, 4 mg, and the others	Kyowa Kirin Co., Ltd., and the others	April 1998	Hypertension
10	Lisinopril hydrate	Zestril Tablets 5, 10, 20, and the others Longes Tablets 5 mg, 10 mg, 20 mg, and the others	AstraZeneca K.K., and the others Kyowa Pharmaceutical Industry Co., Ltd., and the others	August 1991	Hypertension Patients with the following disease who do not sufficiently respond to basic treatment with digitalis preparations, diuretics, etc.: Chronic cardiac failure (mild to moderate cases)

Preparations containing angiotensin II receptor blocker

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
11	Azilsartan	Azilva Tablets 10 mg, 20 mg, 40 mg, Azilva Granules 1%, and the others	Takeda Pharmaceutical Company Limited., and the others	<Tablets 10 mg> June 2014 <Tablets 20 mg, 40 mg> May 2012 <Granules 1%> December 2021	Hypertension
12	Irbesartan	Avapro Tablets 50 mg, 100 mg, 200 mg, and the others	Sumitomo Pharma Co., Ltd., and the others	<Tablets 50 mg, 100 mg> July 2008	Hypertension
		Irbetan Tablets 50 mg, 100 mg, 200 mg, and the others	Shionogi Pharma Co., Ltd., and the others	<Tablets 200 mg> June 2013	
13	Olmesartan medoxomil	Olmotec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg, and the others	Daiichi Sankyo Co., Ltd., and the others	<OD Tablets 5 mg> June 2017 <OD Tablets 10 mg, 20 mg, 40 mg> December 2015	Hypertension
14	Candesartan cilexetil	Blopress Tablets 2, 4, 8, 12, and the others	Teva Takeda Pharma 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:

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
					Chronic cardiac failure (mild to moderate cases)
15	Telmisartan	Micardis Tablets 20 mg, 40 mg, 80 mg, and the others	Boehringer Ingelheim Japan, Inc., and the others	<Tablets 20 mg, 40 mg> January 2005 <Tablets 80 mg> October 2010	Hypertension
16	Valsartan	Diovan OD Tablets 20 mg, 40 mg, 80 mg, 160 mg, Diovan Tablets 20 mg, 40 mg, 80 mg, 160 mg, and the others	Novartis Pharma K.K., and the others	<OD Tablets> July 2013 <Tablets 20 mg, 40 mg, 80 mg> November 2000 <Tablets 160 mg> December 2004	Hypertension
17	Losartan potassium	Nu-Lotan Tablets 25 mg, 50 mg, 100 mg, and the others	Organon K.K., and the others	<Tablets 25 mg, 50 mg> August 1998 <Tablets 100 mg> March 2009	Hypertension Diabetic nephropathy in type 2 diabetes mellitus accompanied by hypertension and proteinuria
18	Azilsartan/ amlodipine besilate	Zacras Combination Tablets LD, HD, and the others	Takeda Pharmaceutical Company Limited., and the others	June 2014	Hypertension
19	Irbesartan/ amlodipine besilate	Aimix Combination Tablets LD, HD, and the others	Sumitomo Pharma Co., Ltd., and the others	December 2012	Hypertension

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
20	Irbesartan/ trichlormethiazide	Irtra Combination Tablets LD, HD	Shionogi Pharma Co., Ltd.	September 2013	Hypertension
21	Olmesartan medoxomil/ azelnidipine	Rezaltas Combination Tablets LD, HD	Daiichi Sankyo Co., Ltd.	April 2010	Hypertension
22	Candesartan cilexetil/ amlodipine besilate	Unisia Combination Tablets LD, HD, and the others	Teva Takeda Pharma Ltd., and the others	June 2010	Hypertension
23	Candesartan cilexetil/ hydrochlorothiazide	Ecard Combination Tablets LD, HD, and the others	Teva Takeda Pharma Ltd., and the others	March 2009	Hypertension
24	Telmisartan/ amlodipine besilate	Micamlo Combination Tablets AP, BP, and the others	Boehringer Ingelheim Japan, Inc., and the others	<Tablets AP> October 2010 <Tablets BP> May 2013	Hypertension
25	Telmisartan/ amlodipine besilate/ hydrochlorothiazide	Micatrio Combination Tablets	Boehringer Ingelheim Japan, Inc.	November 2016	Hypertension
26	Telmisartan/ hydrochlorothiazide	Micombi Combination Tablets AP, BP, and the others	Boehringer Ingelheim Japan, Inc., and the others	June 2009	Hypertension
27	Valsartan/ amlodipine besilate	Exforge Combination OD Tablets, Exforge Combination Tablets, and the others	Novartis Pharma K.K., and the others	<Tablets> April 2010 <OD Tablets> June 2015	Hypertension

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
28	Valsartan/cilnidipine	Atedio Combination Tablets	EA Pharma Co., Ltd.	May 2014	Hypertension
29	Valsartan/ hydrochlorothiazide	Co-Dio Combination Tablets MD, EX, and the others	Novartis Pharma K.K., and the others	March 2009	Hypertension
30	Losartan potassium/ hydrochlorothiazide	Preminent Tablets LD, HD, and the others	Organon K.K., and the others	<Tablets LD> December 2006 <Tablets HD> April 2014	Hypertension

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Angiotensin receptor-neprilysin inhibitor

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
31	Sacubitril valsartan sodium hydrate	Entresto Tablets 50 mg, 100 mg, 200 mg	Novartis Pharma K.K.	August 2020	<Tablets 50 mg, 100 mg, 200 mg> Chronic cardiac failure The use is limited to patients receiving standard treatment of chronic heart failure. <Tablets 100 mg, 200 mg> Hypertension

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Direct renin inhibitor

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

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