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.
<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 foetuses 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 foetuses 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 foetuses 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.
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.

†: 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
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).
### Angiotensin-converting enzyme inhibitors

<table>
<thead>
<tr>
<th>No.</th>
<th>Non-proprietary name</th>
<th>Brand name</th>
<th>Marketing authorization holder</th>
<th>Japanese market launch</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alacepril</td>
<td>Cetapril Tablets 25 mg, and the others</td>
<td>Sumitomo Pharma Co., Ltd., and the others</td>
<td>June 1988</td>
<td>Essential hypertension, renal hypertension</td>
</tr>
<tr>
<td>2</td>
<td>Imidapril hydrochloride</td>
<td>Tanatril Tablets 2.5, 5, 10, and the others</td>
<td>Mitsubishi Tanabe Pharma Corporation, and the others</td>
<td>December 1993</td>
<td>Hypertension, renal parenchymal hypertension, Diabetic nephropathy associated with type 1 diabetes mellitus, &lt;Tablets 10&gt; Hypertension, renal parenchymal hypertension</td>
</tr>
<tr>
<td>3</td>
<td>Enalapril maleate</td>
<td>Renivace Tablets 2.5, 5, 10, and the others</td>
<td>Organon K.K., and the others</td>
<td>July 1986</td>
<td>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)</td>
</tr>
<tr>
<td>4</td>
<td>Captopril</td>
<td>Captoril Tablets 12.5 mg, 25 mg, Captoril Fine Granules 5%, and the others</td>
<td>Alfresa Pharma Corporation, and the others</td>
<td>&lt;Captoril Tablets 12.5 mg, 25 mg, Fine Granules 5%&gt; February 1983</td>
<td>&lt;Tablets 12.5 mg, 25 mg, Fine Granules 5%&gt; Essential hypertension, renal hypertension, renovascular hypertension, malignant hypertension</td>
</tr>
<tr>
<td>No.</td>
<td>Non-proprietary name</td>
<td>Brand name</td>
<td>Marketing authorization holder</td>
<td>Japanese market launch</td>
<td>Indications</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------</td>
<td>------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
<td>Captoril hydrochloride</td>
<td>Captoril-R Capsules 18.75 mg</td>
<td>&lt;Captoril-R Capsules 18.75 mg&gt;</td>
<td>February 1989</td>
<td>Essential hypertension, renal hypertension</td>
</tr>
<tr>
<td>2</td>
<td>Temocapril hydrochloride</td>
<td>Acecol Tablets 1 mg, 2 mg, 4 mg, and the others</td>
<td>Alfresa Pharma Corporation, and the others</td>
<td>August 1994</td>
<td>Hypertension, renal parenchymal hypertension, renovascular hypertension</td>
</tr>
<tr>
<td>3</td>
<td>Delapril hydrochloride</td>
<td>Adecut 7.5 mg, 15 mg, 30 mg Tablets</td>
<td>Teva Takeda Pharma Ltd.</td>
<td>April 1989</td>
<td>Essential hypertension, renal hypertension, renovascular hypertension</td>
</tr>
<tr>
<td>4</td>
<td>Trandolapril</td>
<td>Odric Tablets 0.5 mg, 1 mg, and the others</td>
<td>Nippon Shinyaku Co., Ltd., and the others</td>
<td>May 1996</td>
<td>Hypertension</td>
</tr>
<tr>
<td>5</td>
<td>Benazepril hydrochloride</td>
<td>Cibacen Tablets 2.5 mg, 5 mg, 10 mg, and the others</td>
<td>Sun Pharma Japan Limited., and the others</td>
<td>April 1993</td>
<td>Hypertension</td>
</tr>
<tr>
<td>6</td>
<td>Perindopril erbumine</td>
<td>Coversyl Tablets 2 mg, 4 mg, and the others</td>
<td>Kyowa Kirin Co., Ltd., and the others</td>
<td>April 1998</td>
<td>Hypertension</td>
</tr>
<tr>
<td>7</td>
<td>Lisinopril hydrate</td>
<td>Zestril Tablets 5, 10, 20, and the others</td>
<td>AstraZeneca K.K., and the others</td>
<td>August 1991</td>
<td>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)</td>
</tr>
</tbody>
</table>

Preparations containing angiotensin II receptor blocker

Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp
<table>
<thead>
<tr>
<th>No.</th>
<th>Non-proprietary name</th>
<th>Brand name</th>
<th>Marketing authorization holder</th>
<th>Japanese market launch</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Azilsartan</td>
<td>Azilva Tablets 10 mg, 20 mg, 40 mg, Azilva Granules 1%, and the others</td>
<td>Takeda Pharmaceutical Company Limited., and the others</td>
<td>&lt;Tablets 10 mg&gt; June 2014 &lt;Tablets 20 mg, 40 mg&gt; May 2012 &lt;Granules 1%&gt; December 2021</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Irbesartan</td>
<td>Avapro Tablets 50 mg, 100 mg, 200 mg, and the others</td>
<td>Sumitomo Pharma Co., Ltd., and the others</td>
<td>&lt;Tablets 50 mg, 100 mg&gt; July 2008</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irbetan Tablets 50 mg, 100 mg, 200 mg, and the others</td>
<td>Shionogi Pharma Co., Ltd., and the others</td>
<td>&lt;Tablets 200 mg&gt; June 2013</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Olmesartan medoxomil</td>
<td>Olmetec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg, and the others</td>
<td>Daiichi Sankyo Co., Ltd., and the others</td>
<td>&lt;OD Tablets 5 mg&gt; June 2017 &lt;OD Tablets 10 mg, 20 mg, 40 mg&gt; December 2015</td>
<td>Hypertension</td>
</tr>
<tr>
<td>14</td>
<td>Candesartan cilexetil</td>
<td>Blopress Tablets 2, 4, 8, 12, and the others</td>
<td>Teva Takeda Pharma Ltd., and the others</td>
<td>June 1999</td>
<td>&lt;Tablets 2, 4, 8, 12&gt; Hypertension, renal parenchymal hypertension &lt;Tablets 2, 4, 8&gt; Patients with the following disease to whom administration of angiotensin-converting enzyme inhibitors is not appropriate:</td>
</tr>
<tr>
<td>No.</td>
<td>Non-proprietary name</td>
<td>Brand name</td>
<td>Marketing authorization holder</td>
<td>Japanese market launch</td>
<td>Indications</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------</td>
<td>------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>15</td>
<td>Telmisartan</td>
<td>Micardis Tablets 20 mg, 40 mg, 80 mg, and the others</td>
<td>Boehringer Ingelheim Japan, Inc., and the others</td>
<td>January 2005/ Tablets 20 mg, 40 mg October 2010/ Tablets 80 mg</td>
<td>Chronic cardiac failure (mild to moderate cases)</td>
</tr>
<tr>
<td>16</td>
<td>Valsartan</td>
<td>Diovan OD Tablets 20 mg, 40 mg, 80 mg, 160 mg, Diovan Tablets 20 mg, 40 mg, 80 mg, 160 mg, and the others</td>
<td>Novartis Pharma K.K., and the others</td>
<td>July 2013/ OD Tablets&gt; December 2004/ Tablets 20 mg, 40 mg, 80 mg November 2000/ Tablets 160 mg</td>
<td>Hypertension</td>
</tr>
<tr>
<td>17</td>
<td>Losartan potassium</td>
<td>Nu-Lotan Tablets 25 mg, 50 mg, 100 mg, and the others</td>
<td>Organon K.K., and the others</td>
<td>August 1998/ Tablets 25 mg, 50 mg March 2009/ Tablets 100 mg</td>
<td>Hypertension Diabetic nephropathy in type 2 diabetes mellitus accompanied by hypertension and proteinuria</td>
</tr>
<tr>
<td>18</td>
<td>Azilsartan/ amlodipine besilate</td>
<td>Zacras Combination Tablets LD, HD, and the others</td>
<td>Takeda Pharmaceutical Company Limited., and the others</td>
<td>June 2014</td>
<td>Hypertension</td>
</tr>
<tr>
<td>19</td>
<td>Irbesartan/ amlodipine besilate</td>
<td>Aimix Combination Tablets LD, HD, and the others</td>
<td>Sumitomo Pharma Co., Ltd., and the others</td>
<td>December 2012</td>
<td>Hypertension</td>
</tr>
<tr>
<td>No.</td>
<td>Non-proprietary name</td>
<td>Brand name</td>
<td>Marketing authorization holder</td>
<td>Japanese market launch</td>
<td>Indications</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------------------</td>
<td>-----------------------------------</td>
<td>------------------------------------------------</td>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>20</td>
<td>Irbesartan/ trichlormethiazide</td>
<td>Irtra Combination Tablets LD, HD</td>
<td>Shionogi Pharma Co., Ltd.</td>
<td>September 2013</td>
<td>Hypertension</td>
</tr>
<tr>
<td>21</td>
<td>Olmesartan medoxomil/ azelnidipine</td>
<td>Rezaltas Combination Tablets LD, HD</td>
<td>Daiichi Sankyo Co., Ltd.</td>
<td>April 2010</td>
<td>Hypertension</td>
</tr>
<tr>
<td>22</td>
<td>Candesartan cilexetil/ amlodipine besilate</td>
<td>Unisia Combination Tablets LD, HD, and the others</td>
<td>Teva Takeda Pharma Ltd., and the others</td>
<td>June 2010</td>
<td>Hypertension</td>
</tr>
<tr>
<td>23</td>
<td>Candesartan cilexetil/ hydrochlorothiazide</td>
<td>Ecard Combination Tablets LD, HD, and the others</td>
<td>Teva Takeda Pharma Ltd., and the others</td>
<td>March 2009</td>
<td>Hypertension</td>
</tr>
<tr>
<td>24</td>
<td>Telmisartan/ amlodipine besilate</td>
<td>Micamlo Combination Tablets AP, BP, and the others</td>
<td>Boehringer Ingelheim Japan, Inc., and the others</td>
<td>&lt;Tablets AP&gt; October 2010</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;Tablets BP&gt; May 2013</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Telmisartan/ amlodipine besilate/ hydrochlorothiazide</td>
<td>Micatrio Combination Tablets</td>
<td>Boehringer Ingelheim Japan, Inc.</td>
<td>November 2016</td>
<td>Hypertension</td>
</tr>
<tr>
<td>26</td>
<td>Telmisartan/ hydrochlorothiazide</td>
<td>Micombi Combination Tablets AP, BP, and the others</td>
<td>Boehringer Ingelheim Japan, Inc., and the others</td>
<td>June 2009</td>
<td>Hypertension</td>
</tr>
<tr>
<td>27</td>
<td>Valsartan/ amlodipine besilate</td>
<td>Exforge Combination OD Tablets, Exforge Combination Tablets, and the others</td>
<td>Novartis Pharma K.K., and the others</td>
<td>&lt;Tablets&gt; April 2010</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;OD Tablets&gt; June 2015</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Non-proprietary name</td>
<td>Brand name</td>
<td>Marketing authorization holder</td>
<td>Japanese market launch</td>
<td>Indications</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>28</td>
<td>Valsartan/cilnidipine</td>
<td>Atedio Combination Tablets</td>
<td>EA Pharma Co., Ltd.</td>
<td>May 2014</td>
<td>Hypertension</td>
</tr>
<tr>
<td>29</td>
<td>Valsartan/ hydrochlorothiazide</td>
<td>Co-Dio Combination Tablets MD, EX, and the others</td>
<td>Novartis Pharma K.K., and the others</td>
<td>March 2009</td>
<td>Hypertension</td>
</tr>
<tr>
<td>30</td>
<td>Losartan potassium/ hydrochlorothiazide</td>
<td>Preminent Tablets LD, HD, and the others</td>
<td>Organon K.K., and the others</td>
<td>&lt;Tablets LD&gt; December 2006 &lt;Tablets HD&gt; April 2014</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>
### Angiotensin receptor-neprilysin inhibitor

<table>
<thead>
<tr>
<th>No.</th>
<th>Non-proprietary name</th>
<th>Brand name</th>
<th>Marketing authorization holder</th>
<th>Japanese market launch</th>
<th>Indications</th>
</tr>
</thead>
</table>
| 31  | Sacubitril valsartan sodium hydrate   | Entresto Tablets     | 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 |
### Direct renin inhibitor

<table>
<thead>
<tr>
<th>No.</th>
<th>Non-proprietary name</th>
<th>Brand name</th>
<th>Marketing authorization holder</th>
<th>Japanese market launch</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Alikiren fumarate</td>
<td>Rasilez Tablets 150 mg</td>
<td>OrphanPacific, Inc.</td>
<td>October 2009</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>