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# Summary of investigation results

## Products Containing Amlodipine Besilate

January 12, 2016

**Non-proprietary name**

a. Amlodipine Besilate
b. Azilsartan/Amlodipine Besilate
c. Aliskiren Fumarate/Amlodipine Besilate
d. Irbesartan/Amlodipine Besilate
e. Telmisartan/Amlodipine Besilate
f. Candesartan Cilexetil/Amlodipine Besilate
g. Valsartan/Amlodipine Besilate
h. Amlodipine Besilate/Atorvastatin Calcium Hydrate

**Brand name (Marketing authorization holder)**

a. Norvasc Tablets 2.5 mg, 5 mg, and 10mg, Norvasc OD Tablets 2.5 mg, 5 mg, and 10 mg (Pfizer Japan Inc.), Amlodin Tablets 2.5 mg, 5 mg, and 10 mg, Amlodin OD Tablets 2.5 mg, 5 mg, and 10 mg (Sumitomo Dainippon Pharma Co., Ltd.), and the others
b. Zacras Combination Tablets LD and HD (Takeda Pharmaceutical Co., Ltd.)
c. Rasilamlo Combination Tablets LD and HD (Novartis Pharma K.K.)
d. Aimix Combination Tablets LD and HD (Sumitomo Dainippon Pharma Co., Ltd.)
e. Micamlo Combination Tablets AP and BP (Nippon Boehringer Ingelheim Co., Ltd.)
f. Unisia Combination Tablets LD and HD (Takeda Pharmaceutical Co., Ltd.) and the others
g. Exforge Combination Tablets, Exforge Combination OD Tablets (Novartis Pharma K.K.) and the others
h. Caduet Combination Tablets No. 1, No. 2, No. 3, and No. 4 (Pfizer Japan Inc.) and the others

**Indications**

Products a are indicated for hypertension and angina pectoris

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Products b to g are indicated for hypertension

Product h is indicated for the following patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Patients with hypertension or angina pectoris, and concurrently with hypercholesterolemia or familial hypercholesterolemia

**Summary of revision**

1. “Fulminant hepatitis” should be added to the “hepatic function disorder and jaundice” subsection in the Clinically significant adverse reaction section for the above products a to f.
   “Fulminant hepatitis” should be added to the “hepatitis, hepatic function disorder, and jaundice” subsection in the Clinically significant adverse reaction section for the above product g.
   “Fulminant hepatitis” should be added to the “hepatic function disorder and jaundice” subsection in the Clinically significant adverse reaction section of amlodipine besilate for the above product h.
2. “Agranulocytosis” should be added to the “thrombocytopenia and leukopenia” subsection in the Clinically significant adverse reaction section for the above products a to e.
   “Agranulocytosis” should be added to the “thrombocytopenia and leukopenia” subsection in the Clinically significant adverse reaction section of amlodipine besilate for the above product h.
3. “Rhabdomyolysis” should be newly added in the Clinically significant adverse reaction section for the above products a to c.
   Precautions regarding occurrence of acute kidney injury should be added to the “rhabdomyolysis” subsection in the Clinically significant adverse reaction section for the above products d to g.
   “Rhabdomyolysis” should be newly added in the Clinically significant adverse reaction section of amlodipine besilate for the above product h.

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**Background of the revision and investigation results**

Cases of fulminant hepatitis, agranulocytosis, and rhabdomyolysis have been reported in patients treated with products containing amlodipine besilate in Japan. Following an investigation result based on the opinions of expert advisors and the available evidence, the MHLW/PMDA concluded that revision of the package insert was necessary.

**The number of reported adverse reaction and fatal cases in the last 3 fiscal years in Japan**

1. Fulminant hepatitis
    a. Amlodipine besilate
        A total of 2 cases with fulminant hepatitis have been reported (including 1 case for which a causal relationship to the product could not be ruled out).
        Both cases had a fatal outcome (the causal relationship between the product and the fatal outcome could not be ruled out for 1 of these patients).
    b. Azilsartan/amlodipine besilate
        No case of fulminant hepatitis has been reported.
    c. Aliskiren fumarate/amlodipine besilate
        No case of fulminant hepatitis has been reported.
    d. Irbesartan/amlodipine besilate
        No case of fulminant hepatitis has been reported.
    e. Telmisartan/amlodipine besilate
        No case of fulminant hepatitis has been reported.
    f. Candesartan cilexetil/amlodipine besilate
        No case of fulminant hepatitis has been reported.
    g. Valsartan/amlodipine besilate
        No case of fulminant hepatitis has been reported.
    h. Amlodipine besilate/atorvastatin calcium hydrate
        No case of fulminant hepatitis has been reported.
2. Agranulocytosis associated cases
    a. Amlodipine besilate
        A case associated with agranulocytosis has been reported (a causal relationship to the product could not be ruled out). No fatality has been reported.
    b. Azilsartan/amlodipine besilate
        No case associated with agranulocytosis has been reported.
    c. Aliskiren fumarate/amlodipine besilate

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No case associated with agranulocytosis been reported.

d. Irbesartan/amlodipine besilate
No case associated with agranulocytosis has been reported.

e. Telmisartan/amlodipine besilate
No case associated with agranulocytosis has been reported.

h. Amlodipine besilate/atorvastatin calcium hydrate
No case associated with agranulocytosis has been reported.

3. Rhabdomyolysis associated cases

a. Amlodipine besilate
A total of 3 cases associated with rhabdomyolysis have been reported (including 1 case for which a causal relationship to the product could not be ruled out). No fatality has been reported.

b. Azilsartan/amlodipine besilate
A case associated with rhabdomyolysis has been reported (a causal relationship to the product could not be ruled out). No fatality has been reported.

c. Aliskiren fumarate/amlodipine besilate
No case associated with rhabdomyolysis been reported.

h. Amlodipine besilate/atorvastatin calcium hydrate
A total of 6 cases associated with rhabdomyolysis have been reported*. No fatality has been reported.

*Causality of rhabdomyolysis and the product had not be evaluated.