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

Diuretics (carbonic anhydrase inhibitors (oral dosage form, injections), thiazide diuretics, loop diuretics)

May 20, 2025

Non-proprietary name

a. Acetazolamide
b. Acetazolamide sodium
c. Indapamide
d. Mefruside
e. Hydrochlorothiazide
f. Benzylhydrochlorothiazide
g. Trichlormethiazide
h. Furosemide
i. Torasemide
j. Azosemide
k. Candesartan cilexetil/hydrochlorothiazide
l. Telmisartan/hydrochlorothiazide
m. Telmisartan/amlodipine besilate/hydrochlorothiazide
n. Valsartan/hydrochlorothiazide
o. Losartan potassium/hydrochlorothiazide
p. Irbesartan/trichlormethiazide

Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

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Indications

See attachment.

Summary of revisions

a., b., c.

1. Precautions for acute myopia, angle closure glaucoma, and choroidal effusion should be added to 8. IMPORTANT PRECAUTIONS.
2. “Acute myopia, angle closure glaucoma, choroidal effusion” should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

e., k. to o.

1. Precautions for acute myopia, angle closure glaucoma, and choroidal effusion should be added to 8. IMPORTANT PRECAUTIONS.
2. “Choroidal effusion” should be added to “acute myopia, angle closure glaucoma” in the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

d., f., g., p.

It should be added to the 15.1 Information Based on Clinical Use section in 15. OTHER PRECAUTIONS that it has been reported that acute myopia, angle closure glaucoma, and/or choroidal effusion occurred in patients treated with other thiazide drugs.

h., i., j.

1. The necessity of adding precautions for acute myopia, angle closure glaucoma, and choroidal effusion to 8. IMPORTANT PRECAUTIONS was discussed.
2. The necessity of adding “acute myopia, angle closure glaucoma, choroidal effusion” to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS was discussed.

Investigation results and background of the revision

For thiazide diuretics (including thiazide-like diuretics) and diuretics containing acetazolamide, risk assessment has been performed or measures have been taken overseas (the US, the EU, Canada, etc.) regarding acute myopia, angle closure glaucoma, and choroidal effusion. There have been reports[*1] in which a relationship between drugs with sulfonamide structure and risks of acute myopia, angle closure glaucoma, and choroidal effusion was suggested.

In light of these findings, for carbonic anhydrase inhibitors (oral dosage form, injections), thiazide diuretics, and loop diuretics, which have a sulfonamide structure among diuretics, cases of adverse reactions reported in Japan and overseas involving acute myopia, angle closure glaucoma, and/or choroidal effusion, as well as published literature, were evaluated.[*2] As a result of consultation with expert advisors, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary, taking into consideration the following:

a., b.

Cases for which a causal relationship of acetazolamide to acute myopia, angle closure glaucoma, and/or choroidal effusion was reasonably possible have been reported in overseas case reports of adverse reactions and in published literature[*3], with multiple reported cases for each event.

c.

Cases for which a causal relationship of indapamide to acute myopia, angle closure glaucoma, and/or choroidal effusion was reasonably possible have been reported in case reports of adverse reactions in Japan and overseas, with several reported cases for each event.

e., k. to o.

Cases for which a causal relationship between hydrochlorothiazide and choroidal effusion was reasonably possible have been reported in several case reports in published literature.[*4]

d., f., g., p.

No cases for which a causal relationship to acute myopia, angle closure glaucoma, or choroidal effusion was reasonably possible have been reported for these drugs, which are classified as thiazide drugs. However, cases for which a causal relationship was reasonably possible have been reported in patients treated with other thiazide drugs.

For other drug preparations, it was determined that revisions of PRECAUTIONS were not necessary at this point for the following reasons:

h.

The number of cases reported in overseas case reports of adverse reactions for which a causal relationship to angle closure glaucoma or choroidal effusion was reasonably possible was limited, with 1 reported case each for each event.

i., j.

No cases have been reported for which a causal relationship of these drugs to acute myopia,

angle closure glaucoma, or choroidal effusion was reasonably possible.

Reference: Number of cases[*5,*6] and patient mortalities involving acute myopia, angle closure glaucoma, and/or choroidal effusion reported in Japan and overseas

a.

No cases have been reported in Japan to date.

A total of 5 cases have been reported overseas to date. (A causal relationship between the drug and the event was reasonably possible for all the 5 cases, in which the drug was administered outside the approved indications.)

No patient mortalities have been reported overseas to date.

c.

A total of 2 cases have been reported in Japan to date. (A causal relationship between the drug and the event was reasonably possible for these cases.)

No patient mortalities have been reported in Japan to date.

A total of 10 cases have been reported overseas to date (including 4 cases for which a causal relationship between the drug and the event was reasonably possible).

No patient mortalities have been reported overseas to date.

h.

No cases have been reported in Japan to date.

A total of 4 cases have been reported overseas to date (including 2 cases for which a causal relationship between the drug and the event was reasonably possible).

No patient mortalities have been reported overseas to date.

o.

No cases have been reported in Japan to date.

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

No patient mortalities have been reported overseas to date.

b., d. to g., i. to n., p.

No cases have been reported to date.

*1 Ah-kee EY, et al.: Qatar Med J. 2015; 2015(1): 6.

*2 For preparations containing hydrochlorothiazide, precautions for acute myopia and angle closure glaucoma have already been included in the Clinically Significant Adverse Reactions section. Therefore, cases involving choroidal effusion were evaluated.

*3 Pathak-Ray V, et al.: Am J Ther. 2020; 27(6): e680-e682

*4 Lee GC et al, Clin Exp Ophthalmol. 2007; 35(1): 55-58: (Case1)

*5 Cases of each event of acute myopia, angle closure glaucoma, and choroidal effusion were retrieved from those collected in the PMDA's database for adverse drug reactions, etc. reports using the search terms “PT: Acute myopia, Myopia, Visual acuity reduced,” “PT: Angle closure glaucoma, Eye pain, Ocular hypertension, Flat anterior chamber of eye, Narrow anterior chamber angle, Glaucoma, Vision blurred,” and “PT: Choroidal effusion, Choroidal detachment, Retinal detachment,” respectively (MedDRA ver28.0). Among them, cases were selected for which confirmation of the event by ophthalmologic tests is described in the column of clinical course.

*6 As for the number of cases for which a causal relationship between the drug and the event was reasonably possible, a case for which a causal relationship of the drug to at least one of the events of acute myopia, angle closure glaucoma, and choroidal effusion was determined to be reasonably possible was counted as 1 case. Of note, for drugs for which cases of the events with a reasonable causal relationship to the drug have been reported, excluding furosemide, more than 1 case has been reported for each event of acute myopia, angle closure glaucoma, and choroidal effusion for which a causal relationship to the drug was reasonably possible.

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 1

No.	Non-proprietary name	Brand name (marketing authorization holder)	Japanese market launch	Indications
a.	Acetazolamide	Diamox Powder, Diamox Tablets 250 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)	(Powder) August 1958 (Tablets) March 1955	(Powder) Glaucoma, epilepsy (to be added when other antiepileptics are not sufficiently effective), improvement of respiratory acidosis in emphysema, cardiac induced oedema, hepatic induced oedema, pre-menstrual tension, Meniere's disease and syndrome (Tablets) Glaucoma, epilepsy (to be added when other antiepileptics are not sufficiently effective), improvement of respiratory acidosis in emphysema, cardiac induced oedema, hepatic induced oedema, pre-menstrual tension, Meniere's disease and syndrome, sleep apnoea syndrome
b.	Acetazolamide sodium	Diamox for Injection 500 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)	December 1963	Glaucoma, epilepsy (to be added when other antiepileptics are not sufficiently effective), improvement of respiratory acidosis in emphysema, Meniere's disease and syndrome
c.	Indapamide	Natrix Tablets 1, 2 (Kyoto Pharmaceutical Industries, Ltd.)	(Tablets 1) February 1985 (Tablets 2) December 1990	Essential hypertension
d.	Mefruside	Baycaron Tablets 25 mg (Mitsubishi Tanabe Pharma Corporation) and the others	October 1975	•Diuresis in the following chronic oedema: Cardiac induced oedema, renal induced oedema, hepatic induced oedema •Hypertension (essential, renal)
e.	Hydrochlorothiazide	Hydrochlorothiazide Tablets 12.5 mg “Towa,” 25 mg “Towa,” Hydrochlorothiazide OD Tablets 12.5 mg “Towa” (Towa Pharmaceutical Co., Ltd.)	(Tablets 12.5 mg) June 2012 (Tablets 25 mg) April 1978 (OD Tablets) December 2013	Hypertension (essential, renal, etc.), malignant hypertension, cardiac induced oedema (congestive cardiac failure), renal induced oedema, hepatic induced oedema, pre-menstrual tension, oedema caused by drugs (corticosteroids, phenylbutazone, etc.)
f.	Benzylhydrochlorothiazide	Behyd Tablets 4 mg (Kyorin Pharmaceutical Co., Ltd.)	February 1961	Hypertension (essential, renal, etc.), malignant hypertension, cardiac induced oedema (congestive cardiac failure), renal induced oedema, hepatic induced oedema
g.	Trichlormethiazide	Fluitran Tablets 1 mg, 2 mg (Shionogi Pharma Co., Ltd.), and the others	(1 mg) May 2009 (2mg) November 1960	Hypertension (essential, renal, etc.), malignant hypertension, cardiac induced oedema (congestive cardiac failure), renal induced oedema, hepatic induced oedema, pre-menstrual tension

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h.	Furosemide	Lasix Injection 20 mg, 100 mg, Lasix Tablets 10 mg, 20 mg, 40 mg (Sanofi K.K.), and the others	(Injection 20mg, Tablets 40 mg) May 1965 (Injection 100mg, Tablets 20 mg) September 1981 (Tablets 10 mg) June 2011	(Injection 20 mg) Hypertension (essential, renal, etc.), malignant hypertension, cardiac induced oedema (congestive cardiac failure), renal induced oedema, hepatic induced oedema, brain oedema, promotion of excretion of urinary calculi (Tablets) Hypertension (essential, renal, etc.), malignant hypertension, cardiac induced oedema (congestive cardiac failure), renal induced oedema, hepatic induced oedema, pre-menstrual tension, oedema due to peripheral vascular disorder, promotion of excretion of urinary calculi (Injection 100 mg) Oliguria due to acute or chronic renal failure
i.	Torasemide	Luprac Tablets 4 mg, 8 mg (Mitsubishi Tanabe Pharma Corporation), and the others	December 1999	Cardiac induced oedema, renal induced oedema, hepatic induced oedema
j.	Azosemide	Diart Tablets 30 mg, 60 mg (Sanwa Kagaku Kenkyusho Co., Ltd.), and the others	(30 mg) June 1993 (60 mg) July 1987	Cardiac induced oedema (congestive cardiac failure), renal induced oedema, hepatic induced oedema
k.	Candesartan cilexetil/ hydrochlorothiazide	Ecard Combination Tablets LD, HD (Teva Takeda Yakuhin Ltd.), and the others	March 2009	Hypertension
l.	Telmisartan/ hydrochlorothiazide	Micombi Combination Tablets AP, BP (Nippon Boehringer Ingelheim Co., Ltd.), and the others	June 2009	Hypertension
m.	Telmisartan/ amlodipine besilate/ hydrochlorothiazide	Micatrio Combination Tablets (Nippon Boehringer Ingelheim Co., Ltd.)	November 2016	Hypertension
n.	Valsartan/ hydrochlorothiazide	Co-DIO Combination Tablets MD, EX (Novartis Pharma K.K.), and the others	March 2009	Hypertension
o.	Losartan potassium/ hydrochlorothiazide	Preminent Tablets LD, HD (Organon K.K.), and the others	(LD) December 2006 (HD) April 2014	Hypertension
p.	Irbesartan/ trichlormethiazide	Irtra Combination Tablets LD, HD (Shionogi Pharma Co., Ltd.)	September 2013	Hypertension