



# Summary of Investigation Results

## Preparations containing amoxicillin hydrate

May 8, 2024

### Non-proprietary name

- a. Amoxicillin hydrate
- b. Potassium clavulanate/amoxicillin hydrate
- c. Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
- d. Vonoprazan fumarate/amoxicillin hydrate/metronidazole
- e. Rabeprazole sodium/amoxicillin hydrate/clarithromycin
- f. Rabeprazole sodium/amoxicillin hydrate/metronidazole

### Brand name (marketing authorization holder)

- a. Sawacillin Capsules 125, 250, Sawacillin Fine Granules 10%, Sawacillin Tablets 250 (LTL Pharma Co., Ltd), and the others
- b. Augmentin Combination Tablets 125SS, 250RS, Clavamox Combination Dry Syrup for Pediatric (GlaxoSmithKline K.K.)
- c. Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited)
- d. Vonopion Pack (Takeda Pharmaceutical Company Limited)
- e. Rabecure Pack 400, 800 (Eisai Co., Ltd.)
- f. Rabefine Pack (Eisai Co., Ltd.)

### Japanese market launch

See attachment.

### Indications

See attachment.

### Summary of revisions

Pharmaceuticals and Medical Devices Agency

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a., b.

1. “Drug-induced enterocolitis syndrome” should be added to the precautions concerning shock, etc. in the 8. IMPORTANT PRECAUTIONS section.
2. “Drug-induced enterocolitis syndrome” should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

c.-f.

1. “Drug-induced enterocolitis syndrome” should be added to the precautions concerning shock, etc. in <Amoxicillin hydrate> in the 8. IMPORTANT PRECAUTIONS section.
2. “Drug-induced enterocolitis syndrome” should be added to <Amoxicillin hydrate> in the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

#### **Investigation results and background of the revision**

Cases involving drug-induced enterocolitis syndrome were evaluated. Cases for which a causal relationship between preparations containing amoxicillin hydrate and drug-induced enterocolitis syndrome was reasonably possible have been reported. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary.

#### **Reference: Number of cases\* and patient mortalities involving drug-induced enterocolitis syndrome reported in Japan and overseas<sup>†</sup>**

- a. One case has been reported in Japan to date. (A causal relationship between the drug and event could not be established for this case.)  
No patient mortalities have been reported in Japan to date.
- b.-f. No cases have been reported in Japan to date.
- a. A total of 2 cases have been reported overseas to date. (A causal relationship between the drug and event was reasonably possible for these cases.)  
No patient mortalities have been reported overseas to date.
- b. A total of 5 cases have been reported overseas to date. (A causal relationship between the drug and event was reasonably possible for these cases.)



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No patient mortalities have been reported overseas to date.

c.-f. No cases have been reported overseas to date.

\* Cases collected in the PMDA's database for adverse drug reactions, etc. reports

† Cases which were presented as the basis for a revision of Company Core Data Sheet (CCDS) by the marketing authorization holder

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).



	Non-proprietary name	Japanese market launch	Indications
a.	Amoxicillin hydrate	<p>Sawacillin Capsules 125: May 2011</p> <p>Sawacillin Capsules 250: January 1975</p> <p>Sawacillin Tablets 250: November 1981</p>	<p>&lt;Applicable microorganisms&gt;</p> <p>Amoxicillin hydrate-susceptible strains of genus <i>Staphylococcus</i>, genus <i>Streptococcus</i>, <i>Pneumococcus</i>, genus <i>Enterococcus</i>, <i>Neisseria gonorrhoeae</i>, <i>Escherichia coli</i>, <i>Proteus mirabilis</i>, <i>Haemophilus influenzae</i>, <i>Helicobacter pylori</i>, <i>Treponema pallidum</i></p> <p>&lt;Applicable conditions&gt;</p> <p>Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, secondary infections following trauma, thermal burn, and surgical wound, secondary infections of erosions/ulcers, mastitis, osteomyelitis, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, prostatitis (acute/chronic), epididymitis, <i>Neisseria gonorrhoeae</i> infection, syphilis, intrauterine infection, adnexitis, parametritis, dacryocystitis, hordeolum, otitis media, periodontal inflammation, pericoronitis, jaw inflammation, scarlet fever, <i>Helicobacter pylori</i> infection of the stomach after endoscopic treatment for gastric/duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach, idiopathic thrombocytopenic purpura, and early stage of gastric cancer, <i>Helicobacter pylori</i> gastritis</p>
		<p>Sawacillin Fine Granules 10%: January, 1975</p>	<p>&lt;Applicable microorganisms&gt;</p> <p>Amoxicillin hydrate-susceptible strains of genus <i>Staphylococcus</i>, genus <i>Streptococcus</i>, <i>Pneumococcus</i>, genus <i>Enterococcus</i>, <i>Neisseria gonorrhoeae</i>, <i>Escherichia coli</i>, <i>Proteus mirabilis</i>, <i>Haemophilus influenzae</i>, <i>Helicobacter pylori</i>, <i>Treponema pallidum</i></p> <p>&lt;Applicable conditions&gt;</p> <p>Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, secondary infections following trauma, thermal burn, and surgical wound, secondary infections of erosions/ulcers, mastitis, osteomyelitis, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, prostatitis (acute/chronic), epididymitis, <i>Neisseria gonorrhoeae</i> infection, syphilis, intrauterine infection, adnexitis, parametritis, dacryocystitis, hordeolum, otitis media, periodontal inflammation, pericoronitis, jaw inflammation, scarlet fever, <i>Helicobacter pylori</i> infection of the stomach/duodenal ulcer</p>



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b.	Potassium clavulanate/ amoxicillin hydrate	Augmentin Combination Tablets 125SS, 250RS: August 1985	<p>&lt;Applicable microorganisms&gt; Potassium clavulanate/amoxicillin hydrate- susceptible strains of genus <i>Staphylococcus</i>, <i>Neisseria gonorrhoeae</i>, <i>Escherichia coli</i>, genus <i>Klebsiella</i>, genus <i>Proteus</i>, <i>Haemophilus influenzae</i>, genus <i>Bacteroides</i>, genus <i>Prevotella</i> (except <i>Prevotella bivia</i>)</p> <p>&lt;Applicable conditions&gt; Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, pharyngitis/laryngitis, tonsillitis, acute bronchitis, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, <i>Neisseria gonorrhoeae</i> infection, intrauterine infection, adnexitis, otitis media</p>
		Clavamox Combination Dry Syrup for Pediatric January 2006	<p>&lt;Applicable microorganisms&gt; Potassium clavulanate/amoxicillin hydrate- susceptible strains of <i>Pneumococcus</i> (minimum inhibitory concentration equal to or less than 2 µg/mL for penicillin G), <i>Moraxella (Branhamella) catarrhalis</i>, <i>Haemophilus influenza</i>, genus <i>Staphylococcus</i>, <i>Escherichia coli</i>, genus <i>Klebsiella</i>, genus <i>Proteus</i>, genus <i>Bacteroides</i>, genus <i>Prevotella</i> (except <i>Prevotella bivia</i>)</p> <p>&lt;Applicable conditions&gt; Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, pharyngitis/laryngitis, tonsillitis, acute bronchitis, cystitis, pyelonephritis, otitis media, sinusitis</p>
c.	Vonoprazan fumarate/ amoxicillin hydrate/ clarithromycin	June 2016	<p>&lt;Applicable microorganisms&gt; Amoxicillin/clarithromycin-susceptible strains of <i>Helicobacter pylori</i></p> <p>&lt;Applicable conditions&gt; <i>Helicobacter pylori</i> infection of the stomach after endoscopic treatment for gastric/duodenal ulcer, MALT lymphoma of the stomach, idiopathic thrombocytopenic purpura and early stage of gastric cancer, <i>Helicobacter pylori</i> gastritis</p>
d.	Vonoprazan fumarate/ amoxicillin hydrate/ metronidazole	June 2016	<p>&lt;Applicable microorganisms&gt; Amoxicillin/metronidazole-susceptible strains of <i>Helicobacter pylori</i></p> <p>&lt;Applicable conditions&gt; <i>Helicobacter pylori</i> infection of the stomach after endoscopic treatment for gastric/duodenal ulcer, MALT lymphoma of the stomach, idiopathic thrombocytopenic purpura and early stage of gastric cancer, <i>Helicobacter pylori</i> gastritis</p>

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e.	Rabeprazole sodium/ amoxicillin hydrate/ clarithromycin	February 2014	<Applicable microorganisms> Amoxicillin/clarithromycin-susceptible strains of <i>Helicobacter pylori</i> <Applicable conditions> <i>Helicobacter pylori</i> infection of the stomach after endoscopic treatment for gastric/duodenal ulcer, MALT lymphoma of the stomach, idiopathic thrombocytopenic purpura and early stage of gastric cancer, <i>Helicobacter pylori</i> gastritis
f.	Rabeprazole sodium/ amoxicillin hydrate/ metronidazole	February 2014	<Applicable microorganisms> Amoxicillin/metronidazole-susceptible strains of <i>Helicobacter pylori</i> <Applicable conditions> <i>Helicobacter pylori</i> infection of the stomach after endoscopic treatment for gastric/duodenal ulcer, MALT lymphoma of the stomach, idiopathic thrombocytopenic purpura and early stage of gastric cancer, <i>Helicobacter pylori</i> gastritis

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