

Summary of Investigation Results

Preparations containing metronidazole (oral dosage form and injections)

June 14, 2022

Non-proprietary name

- a. Metronidazole
- b. Rabeprazole sodium/amoxicillin hydrate/metronidazole
- c. Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Brand name (Marketing authorization holder)

- a. Flagyl Oral Tablets 250 mg (Shionogi Pharma Co., Ltd.), Anaemetro Intravenous infusion 500 mg (Pfizer Japan Inc.)
- b. Rabefine Pack (Eisai Co., Ltd.)
- c. Vonopion Pack (Takeda Pharmaceutical Company Limited)

Indications

See Attachment

Summary of revisions

a.

“Prolonged QT, ventricular tachycardia (including torsade de pointes)” should be added to the Clinically Significant Adverse Reactions section.

b.-c.

“Prolonged QT, ventricular tachycardia (including torsade de pointes)” should be added to the language concerning metronidazole in the Clinically Significant Adverse Reactions section.

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Investigation results and background of the revision

Cases involving prolonged QT and/or ventricular tachycardia (including torsade de pointes) reported in Japan and overseas were evaluated. Cases for which a causal relationship of metronidazole to prolonged QT and/or ventricular tachycardia (including torsade de pointes) was reasonably possible have been reported overseas. As a result of consultation with expert advisors, MHLW/PMDA concluded that revision of Precautions of preparations containing metronidazole (oral dosage form and injections) was necessary.

Number of cases and patient mortalities of prolonged QT and/or ventricular tachycardia reported in Japan and overseas during the previous 3 fiscal years

- a. 1 case has been reported in Japan to date (A causal relationship between the drug and the event could not be established for this case).

No patient mortalities have been reported in Japan to date.

A total of 11 cases have been reported overseas to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).

No patient mortalities have been reported overseas to date.

- b. No cases have been reported in Japan to date.

No cases have been reported overseas to date.

- c. No cases have been reported in Japan to date.

No cases have been reported overseas to date

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).

No.	Non-proprietary name	Indications
a.	Metronidazole	<p>Oral dosage form</p> <ul style="list-style-type: none"> ● Trichomoniasis (infection with <i>Trichomonas vaginalis</i>) ● Anaerobic bacterial infection <p><Applicable microorganisms></p> <p>Metronidazole-susceptible strains of genus <i>Peptostreptococcus</i>, genus <i>Bacteroides</i>, genus <i>Prevotella</i>, genus <i>Porphyromonas</i>, genus <i>Fusobacterium</i>, genus <i>Clostridium</i>, genus <i>Eubacterium</i></p> <p><Applicable conditions></p> <ul style="list-style-type: none"> • Deep-seated skin infections • Secondary infections following trauma, thermal burn, surgical wound, etc. • Osteomyelitis • Pneumonia, lung abscess • Pelvic inflammatory disease • Peritonitis, intra-abdominal abscess • Liver abscess • Brain abscess

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

No.	Non-proprietary name	Indications
		<ul style="list-style-type: none"> ● Infectious enteritis <Applicable microorganisms> Metronidazole-susceptible strains of <i>Clostridium difficile</i> <Applicable conditions> Infectious enteritis (including pseudomembranous colitis) ● Bacterial vaginosis <Applicable microorganisms> Metronidazole-susceptible strains of genus <i>Peptostreptococcus</i>, <i>Bacteroides fragilis</i>, <i>Prevotella bivia</i>, genus <i>Mobiluncus</i>, <i>Gardnerella vaginalis</i> <Applicable conditions> Bacterial vaginosis ● <i>Helicobacter pylori</i> infection <i>Helicobacter pylori</i> infection in the stomach and <i>Helicobacter pylori</i> gastritis after endoscopic treatment of gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura, or early-stage gastric cancer ● Amoebic dysentery ● <i>Giardia lamblia</i> infection

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No.	Non-proprietary name	Indications
		<p>Injections</p> <ul style="list-style-type: none"> ● Anaerobic bacterial infection <p><Applicable microorganisms></p> <p>Metronidazole-susceptible strains of genus <i>Peptostreptococcus</i>, genus <i>Bacteroides</i>, genus <i>Prevotella</i>, genus <i>Porphyromonas</i>, genus <i>Fusobacterium</i>, genus <i>Clostridium</i>, genus <i>Eubacterium</i></p> <p><Applicable conditions></p> <ul style="list-style-type: none"> • Sepsis • Deep-seated skin infections • Secondary infections following trauma, thermal burn, surgical wound, etc. • Osteomyelitis • Pneumonia, lung abscess, pyothorax • Pelvic inflammatory disease • Peritonitis, intra-abdominal abscess • Cholecystitis, liver abscess • Pyogenic meningitis • Brain abscess

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No.	Non-proprietary name	Indications
		<ul style="list-style-type: none"> ● Infectious enteritis <Applicable microorganisms> Metronidazole-susceptible strains of <i>Clostridium difficile</i> <Applicable conditions> • Infectious enteritis (including pseudomembranous colitis) ● Amoebic dysentery
b.	Rabeprazole sodium/amoxicillin hydrate/metronidazole	<ul style="list-style-type: none"> <Applicable microorganisms> Amoxicillin/metronidazole-susceptible strains of <i>Helicobacter pylori</i> <Applicable conditions> <i>Helicobacter pylori</i> infection in the stomach and <i>Helicobacter pylori</i> gastritis after endoscopic treatment of gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura, or early-stage gastric cancer
c.	Vonoprazan fumarate/amoxicillin hydrate/metronidazole	<ul style="list-style-type: none"> <Applicable microorganisms> Amoxicillin/metronidazole-susceptible strains of <i>Helicobacter pylori</i> <Applicable conditions> <i>Helicobacter pylori</i> infection in the stomach and <i>Helicobacter pylori</i> gastritis after endoscopic treatment of gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, idiopathic

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No.	Non-proprietary name	Indications
		thrombocytopenic purpura, or early-stage gastric cancer

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