



Summary of Investigation Results

Products containing metronidazole

(oral and injectable dosage forms)

June 5, 2018

Non-proprietary name

- a. Metronidazole (oral and injectable dosage forms)
- b. Lansoprazole/amoxicillin hydrate/metronidazole
- c. Rabeprazole sodium/amoxicillin hydrate/metronidazole
- d. Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Branded name (Marketing authorization holder)

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

Indications

See Attachment.

Summary of revisions

- a.
 1. "Patients with Cockayne's syndrome" should be added to the Careful Administration section.
 2. Precautions for hepatic impairment should be added to the Important Precautions section.
 3. "Hepatic Impairment" should be added to the Clinically Significant Adverse Reactions section.



b.-d.

1. “Patients with Cockayne’s syndrome” should be added to the language concerning metronidazole in the Careful Administration section.
2. Precautions regarding hepatic impairment should be added to the language concerning metronidazole in the Important Precautions section.
3. “Hepatic Impairment” should be added to the language concerning metronidazole in the Clinically Significant Adverse Reactions section.

Investigation results and background of revision items

Cases of hepatic impairment have been reported in patients treated with preparations containing metronidazole in Japan. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their investigation of the currently available evidence including information from the relevant scientific literature and in consultation with expert advisors.

Number of adverse reactions and patient mortalities reported in Japan during the previous 3 fiscal years

- a. Metronidazole (oral and injectable dosage forms)
A total of 4 cases involving hepatic impairment have been reported to date (including 2 cases for which a causal relationship with the product could not be ruled out.)
No patient mortalities have been reported to date.
- b. Lansoprazole/amoxicillin hydrate/metronidazole
No cases involving hepatic impairment have been reported to date.
- c. Rabeprazole sodium/amoxicillin hydrate/metronidazole
No cases involving hepatic impairment have been reported to date.
- d. Vonoprazan fumarate/amoxicillin hydrate/metronidazole
No cases involving hepatic impairment have been reported to date.



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Attachment

Non-proprietary Name	Brand name (Marketing authorization holder)	Indications
a. Metronidazole (oral and injectable dosage forms)	Flagyl Oral Tablets 250 mg (Shionogi & Co., Ltd.), Anaemetro Intravenous infusion 500 mg (Pfizer Japan Inc.)	Oral dosage form 1. Trichomoniasis (infection caused by <i>Trichomonas vaginalis</i>) 2. Anaerobic bacterial infection <Applicable microorganisms> 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> , and genus <i>Eubacterium</i> <Applicable conditions> ·Deep-seated skin infections ·Secondary infections following trauma, thermal burn, and surgical wound ·Osteomyelitis ·Pneumonia, lung abscess ·Pelvic inflammatory disease ·Peritonitis, intra-abdominal abscess ·Liver abscess ·Brain abscess 3. Infectious enteritis <Applicable microorganisms> Metronidazole-susceptible strains of <i>Clostridium difficile</i>



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Non-proprietary Name	Brand name (Marketing authorization holder)	Indications
		<p><Applicable conditions> Infectious enteritis (including pseudomembranous colitis)</p> <p>4. 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></p> <p><Applicable conditions> Bacterial vaginosis</p> <p>5. <i>Helicobacter pylori</i> infection <Applicable microorganisms> Metronidazole-susceptible strains of <i>Helicobacter pylori</i></p> <p><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</p> <p>6. Amoebic dysentery</p> <p>7. <i>Giardia lamblia</i> infection</p>



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Non-proprietary Name	Brand name (Marketing authorization holder)	Indications
		<p>Injectable dosage form</p> <p>1. Anaerobic bacterial infection <Applicable microorganisms> 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>, and 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, and surgical wound• Osteomyelitis• Pneumonia, lung abscess, pyothorax• Pelvic inflammatory disease• Peritonitis, intra-abdominal abscess• Cholecystitis, liver abscess• Pyogenic meningitis• Brain abscess <p>2. Infectious enteritis <Applicable microorganisms> Metronidazole-susceptible strains of <i>Clostridium difficile</i></p>



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Non-proprietary Name	Brand name (Marketing authorization holder)	Indications
		<Applicable conditions> Infectious enteritis (including pseudomembranous colitis) 3. Amoebic dysentery
b. Lansoprazole/amoxicillin hydrate/metronidazole	Lampion Pack (Takeda Pharmaceutical Company Limited)	<Applicable microorganisms> Amoxicillin and 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. Rabeprazole sodium/amoxicillin hydrate/metronidazole	Rabefine Pack (Eisai Co., Ltd.)	<Applicable microorganisms> Amoxicillin and 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



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		lymphoma, idiopathic thrombocytopenic purpura, or early-stage gastric cancer
d. Vonoprazan fumarate/amoxicillin hydrate/metronidazole	Vonopion Pack (Takeda Pharmaceutical Company Limited)	<Applicable microorganisms> Amoxicillin and 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