



Summary of investigation results

Warfarin potassium and Azole antifungal drugs (oral, injections)

October 18, 2016

Non-proprietary name

- a. Warfarin potassium
- b. Miconazole (gel, injection)
- c. Itraconazole
- d. Fluconazole
- e. Fosfluconazole
- f. Voriconazole

Brand name (Marketing authorization holder)

- a. Warfarin Tablets 0.5 mg, 1 mg, 5 mg, Warfarin Granules 0.2% (Eisai Co., Ltd.), and the others
- b. Florid Oral Gel 2%, Florid-F 200 mg for Injections (Mochida Pharmaceutical Co., Ltd.)
- c. Itrizole Capsules 50 mg, Itrizole Oral Solution 1%, Itrizole Injection 1% (200 mg) (Janssen Pharmaceutical K.K.), and the others
- d. Diflucan Capsules 50 mg, 100 mg, Diflucan Dry Syrup 350 mg, 1400 mg, Diflucan Intravenous Solution 50 mg, 100 mg, 200 mg (Pfizer Japan Inc.), and the others
- e. Prodif Intravenous Solution 100 mg, 200 mg, 400 mg (Pfizer Japan Inc.)
- f. Vfend Tablets 50 mg, 200 mg, Vfend Dry Syrup 2800 mg, Vfend Intravenous Solution 200 mg (Pfizer Japan Inc.), and the others

Indications

Refer to the attachment below.

Summary of revision

- a.
 1. "Patients receiving miconazole (gel, injection)" should be added in the Contraindications section.



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2. "Miconazole (gel, injection)" should be added in the Contraindications for Concomitant Use subsection.
 - b.
 1. "Patients receiving warfarin potassium" should be added in the Contraindications section.
 2. "Warfarin potassium" should be added in the Contraindications for Concomitant Use subsection.
 - c-f
 1. "Patients receiving warfarin potassium" should be added in the Careful Administration section.
 2. Precautions for concomitant use with warfarin potassium should be added in the Important Precautions section.

Background of the revision and investigation results

With respect to interactions between miconazole (gel, injection) (hereinafter, miconazole) and warfarin potassium (hereinafter, warfarin), precautionary information has been provided in the Careful Administration section, Important Precautions section, and Precautions for Concomitant Use subsection of the package insert of miconazole.

However, a substantial number of cases of serious bleeding during concomitant administration or after discontinuation of concomitant administration have been reported. Marked changes in laboratory values relevant to anticoagulant function (increased PT-INR) has been observed in these cases.

Taking account of following facts and the results of an investigation based on the opinions of expert advisors, the MHLW/PMDA concluded that concomitant administration of miconazole and warfarin should be contraindicated.

1. It would be difficult to avoid the risk of bleeding caused due to the interactions by monitoring of anticoagulant function enhanced even further.
2. In terms of efficacy, other azole antifungal drugs as first-line treatments for oropharyngeal candidiasis, etc., are recommended in the "Clinical Practice Guidelines for Diagnosis and Treatment of Deep-seated Mycoses 2014". As for



miconazole, it is just described as a second-line treatment for oropharyngeal candidiasis, etc.

3. Up to 13 April 2016, Medicines and Healthcare products Regulatory Agency (MHRA) has received Yellow Cards that report possible drug interactions between miconazole and warfarin, including fatal cases due to a haemorrhagic event. MHRA reminded healthcare professionals of the risk of interactions between miconazole and warfarin, and they said they are currently reviewing the available data for this interaction to determine whether further measures are required to minimize the risk.

Due to concomitant administration of miconazole and warfarin is contraindicated, use of other azole antifungal drugs, including those recommended as first-line treatments in the above-stated guideline, is expected in many cases. Considering that caution is also required for concomitant administration of warfarin and other azole antifungal drugs because marked increase in PT-INR have been reported in patients treated with warfarin and other azole antifungal drugs, though small in number in comparison to the estimated number of patients using other azole antifungal drugs, as well as the results of an investigation based on the opinions of expert advisors, MHLW/PMDA concluded that it would be appropriate to revise the package insert of other azole antifungal drugs.

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

The following cases associated with bleeding events have been reported after concomitant administration of the following products

- a + b [warfarin potassium and miconazole (gel, injection)]
A total of 41 cases has been reported (including 31 cases for which a causal relationship to the products could not be ruled out; 2 of these 31 cases occurred after treatment at a dosage and administration that was different from the approved one). One fatal case has been reported (including no case for which a causal relationship to the products could not be ruled out).
- a + c (warfarin potassium and itraconazole)
One case has been reported (including no case for which a causal relationship to the products could not be ruled out). One fatal case has been reported (including no case for which a causal relationship to the products could not be ruled out).

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- a + d (warfarin potassium and fluconazole)
A total of 3 cases has been reported (including 1 case for which a causal relationship to the products could not be ruled out). No fatality has been reported.
- a + e (warfarin potassium and fosfluconazole)
No cases have been reported.
- a + f (warfarin potassium and voriconazole)
One case has been reported (including 1 case for which a causal relationship to the products could not be ruled out). No fatality has been reported.



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Attachment

Non-proprietary name	Brand name	Indications
Warfarin potassium	Warfarin Tablets 0.5 mg, 1 mg, 5 mg; Warfarin Granules 0.2%	Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, slowly progressing cerebral thrombosis, etc.)
Miconazole (gel, injection)	Florid Oral gel 2%	The following infections with <i>Candida</i> species: Oral candidiasis, esophageal candidiasis
	Florid-F 200 mg for Inj.	The following infections with miconazole-susceptible fungi among <i>Cryptococcus</i> , <i>Candida</i> , <i>Aspergillus</i> , and <i>Coccidioides</i> : Fungemia, pulmonary mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis
Itraconazole	Itrizole Capsules 50	<ul style="list-style-type: none">• Applicable microorganisms: <i>Dermatophytes (Trichophyton, Microsporum, Epidermophyton)</i>, <i>Candida</i>, <i>Malassezia</i>, <i>Aspergillus</i>, <i>Cryptococcus</i>, <i>Sporothrix</i>, <i>Fonsecaea</i>• Applicable conditions<ol style="list-style-type: none">(1) Visceral mycosis (deep mycosis) Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis(2) Deep cutaneous mycosis Sporotrichosis, chromomycosis(3) Superficial cutaneous mycosis (excluding tinea unguium)<ul style="list-style-type: none">• Tinea Body tinea, tinea cruris, tinea manuum, tinea pedis, tinea capitis, kerion celsi, tinea barbae• Candidiasis Oral candidiasis, cutaneous candidiasis, nail candidiasis, candidal paronychia and



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		onychial candidiasis, chronic mucocutaneous candidiasis <ul style="list-style-type: none">• Tinea versicolor, Malassezia folliculitis (4) Tinea unguium
	Itrizole Oral Solution 1%	1. Fungal infection <ul style="list-style-type: none">• Applicable microorganisms <i>Aspergillus, Candida, Cryptococcus, Blastomyces, Histoplasma</i>• Applicable conditions Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, oropharyngeal candidiasis, esophageal candidiasis, blastomycosis, histoplasmosis 2. Febrile neutropenia suspected of fungal infection
	Itrizole Injection 1% (200 mg)	1. Fungal infection <ul style="list-style-type: none">• Applicable microorganisms <i>Aspergillus, Candida, Cryptococcus, Blastomyces, Histoplasma</i>• Applicable conditions Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, esophageal candidiasis, blastomycosis, histoplasmosis 2. Febrile neutropenia suspected of fungal infection
Fluconazole	Diflucan Capsules 50 mg, 100 mg	<ul style="list-style-type: none">• The following infections with <i>Candida</i> or <i>Cryptococcus</i>: Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis



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		<ul style="list-style-type: none">• Prophylaxis of deep mycosis in hematopoietic stem cell transplant patients• Vaginitis or vulvovaginitis caused by <i>Candida</i>
	Diflucan Dry Syrup 350 mg, 1400 mg, Diflucan Intravenous Solution 50 mg, 100 mg, 200 mg	<ul style="list-style-type: none">• The following infections with <i>Candida</i> or <i>Cryptococcus</i>: Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis• Prophylaxis of deep mycosis in hematopoietic stem cell transplant patients
Fosfluconazole	Prodif Intravenous Solution 100, 200, 400	<ul style="list-style-type: none">• The following infections with <i>Candida</i> or <i>Cryptococcus</i>: Fungemia, respiratory mycosis, fungal peritonitis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis
Voriconazole	Vfend Tablets 50 mg, 200 mg, Vfend Dry Syrup 2800 mg	The following severe or refractory fungal infections: <ul style="list-style-type: none">• Invasive aspergillosis, pulmonary aspergilloma, chronic necrotizing pulmonary aspergillosis• Candidemia, esophageal candidiasis, candida peritonitis, bronchopulmonary candidiasis• Cryptococcal meningitis, pulmonary cryptococcosis• Fusariosis• Scedosporiosis Prophylaxis of deep mycosis in hematopoietic stem cell transplant patients
	Vfend for Intravenous Use 200 mg	The following severe or refractory fungal infections: <ul style="list-style-type: none">• Invasive aspergillosis, pulmonary aspergilloma, chronic necrotizing pulmonary aspergillosis• Candidemia, candida peritonitis,



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		<p>bronchopulmonary candidiasis</p> <ul style="list-style-type: none">• Cryptococcal meningitis, pulmonary cryptococcosis• Fusariosis• Scedosporiosis <p>Prophylaxis of deep mycosis in hematopoietic stem cell transplant patients</p>
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