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.

Summary of Investigation Results
Antitubercular agents

March 23, 2023

Non-proprietary name

a. Aluminoparaaminosalicylate calcium hydrate

b., c. Isoniazid

d. Isoniazid sodium methanesulfonate hydrate

e., f. Ethambutol hydrochloride

g. Ethionamide

h. Enviomycin sulfate

i. Kanamycin sulfate

j. Cycloserine

k. Streptomycin sulfate

l. Delamanid

m. Calcium paraaminosalicylate hydrate

n. Pyrazinamide

o. Bedaquiline fumarate

p. Rifabutin

q. Rifampicin

r. Levofloxacin hydrate (oral dosage form)

Brand name (marketing authorization holder)

a. Alumino Nippas Calcium Granules 99% (Mitsubishi Tanabe Pharma Corporation)
b. Iscotin Powder, Iscotin Tablets 100 mg, Iscotin Injection 100 mg (Alfresa Pharma Corporation)
c. Hydra Tablet “Otsuka” 50 mg (Otsuka Pharmaceutical Factory, Inc.)
d. Neoiscotin Powder, Neoiscotin Tablets 100 mg (Alfresa Pharma Corporation)
e. Esanbutol Tablets 125 mg, 250 mg (Sandoz K.K.)
f. Ebutol Tablets 125 mg, 250 mg (Kaken Pharmaceutical Co., Ltd.)
g. Tubermin Tablets 100 mg (Meiji Seika Pharma Co., Ltd.)

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

h. Tuberactin Inj. 1 g (Asahi Kasei Pharma Corporation)
i. Kanamycin Sulfate Injection 1000 mg “Meiji” (Meiji Seika Pharma Co., Ltd.)
j. Cycloserine Capsules 250 mg “Meiji” (Meiji Seika Pharma Co., Ltd.)
k. Streptomycin Sulfate 1 g “Meiji” for Injection (Meiji Seika Pharma Co., Ltd.)
l. Deltyba tablets 50 mg (Otsuka Pharmaceutical Co., Ltd.)
m. Nippas Calcium Granules 100% (Mitsubishi Tanabe Pharma Corporation)
n. Pyramide Powder (Alfresa Pharma Corporation)
o. Sirturo Tablets 100 mg (Janssen Pharmaceutical K.K.)
p. Mycobutin Capsules 150 mg (Pfizer Japan Inc.)
q. Rifadin Capsules 150 mg (Daiichi Sankyo Co., Ltd.) and the others
r. Cravit Tablets 250 mg, 500 mg, Cravit Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others

Japanese market launch
See attachment.

Indications
See attachment.

Summary of revisions
A cautionary statement regarding paradoxical drug reactions should be added to the IMPORTANT PRECAUTIONS section.

Investigation results and background of the revision
In response to the revision of US Prescribing Information for some of antitubercular agents, the necessity of a precaution for paradoxical drug reactions was discussed. As a result of consultation with expert advisors on the causality assessment of the cases and the necessity of revision of Precautions, the MHLW/PMDA concluded that revision of Precautions for all the antitubercular agents was necessary based on the following points:
•Paradoxical drug reactions induced by antitubercular agents are already known to healthcare professionals who provide treatment for tuberculosis. In the cases reported in Japan for which a causal relationship between antitubercular agents and paradoxical drug reactions was reasonably possible, no specific problems were observed in treating the event.

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

However, in association with the recent low prevalence of tuberculosis, it is expected that there will be situations in which tuberculosis will be treated at medical institutions other than those designated for this disease and that the number of healthcare professionals who have little experience in treating tuberculosis in Japan will increase.

•The mechanism of a paradoxical drug reaction induced by an antitubercular agent is supposed to involve allergy to a bacterial cell of *Mycobacterium tuberculosis*, and the event may occur during the treatment course of tuberculosis irrespective of the types of the antitubercular agents.

Reference: Number of cases* and patient mortalities involving paradoxical drug reaction reported in Japan

a., d., g.-j., l., m., o., p.

No cases have been reported.

b., c.

A total of 19 cases have been reported to date (including 11 cases for which a causal relationship between the drug and event was reasonably possible).

A total of 2 patient mortalities have been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for any of these cases.)

e., f.

A total of 13 cases have been reported to date (including 7 cases for which a causal relationship between the drug and event was reasonably possible).

1 instance of patient mortality has been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for this case.)

k.

A total of 2 cases have been reported to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).

No patient mortalities have been reported to date.

n.

A total of 17 cases have been reported to date (including 10 cases for which a causal relationship between the drug and event was reasonably possible).

A total of 2 patient mortalities have been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for any of these cases.)

q.

A total of 15 cases have been reported to date (including 8 cases for which a causal relationship between the drug and event was reasonably possible).

1 instance of patient mortality has been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for this case.)

r.

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

No patient mortalities have been reported to date.

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

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).

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.

Attachment

	Non-proprietary name	Japanese market launch	Indications
a.	Aluminoparaaminosalicylate calcium hydrate	August 1956	<Applicable microorganisms> Paraaminosalicylic acid-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
b, c.	Isoniazid	Iscotin Powder: July 1952 (Japanese market launch of “Iscotin”) Iscotin Tablets 100 mg: July 1952 Iscotin Injection 100 mg: July 1954 (Japanese market launch of “Iscotin Injection”)	<Applicable microorganisms> Isoniazid-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
		Hydra Tablet “Otsuka” 50 mg: July 1952	
d.	Isoniazid sodium methanesulfonate hydrate	Neoiscotin Powder, Neoiscotin Tablets 100 mg: July 1954 (Japanese market launch of “Neoiscotin” and “Neoiscotin Tablets”)	<Applicable microorganisms> Isoniazid sodium methanesulfonate hydrate-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
e, f.	Ethambutol hydrochloride	February 1967 (Japanese market launch of “Esanbutol Tablets”)	<Applicable microorganisms> Ethambutol hydrochloride-susceptible strains of genus *Mycobacterium* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis, nontuberculous mycobacteriosis including *Mycobacterium avium* complex (MAC) disease
		Ebutol Tablets 125 mg: January 1967 Ebutol Tablets 250 mg: March 1967	
g.	Ethionamide	September 1961 (Japanese market	<Applicable microorganisms>

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

	Non-proprietary name	Japanese market launch	Indications
		launch of “Tubermin Tablets (100)”)	Ethionamide-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
h.	Enviomycin sulfate	September 1975 (Japanese market launch of “Tuberactin”)	<Applicable microorganisms> Enviomycin-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
i.	Kanamycin sulfate	May 1958 (Japanese market launch of “Kanamycin Sulfate Meiji (injection)”)	<Applicable microorganisms> Kanamycin-susceptible strains of genus *Staphylococcus*, *Pneumococcus*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis, Escherichia coli,* genus *Klebsiella*, genus *Proteus*, *Morganella morganii*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Bordetella pertussis* <Applicable conditions> Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, secondary infections following trauma, thermal burn, and surgical wound, mastitis, osteomyelitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, *Neisseria gonorrhoeae* infection, adnexitis, otitis media, pertussis, pulmonary tuberculosis and other tuberculosis
j.	Cycloserine	July 1964 (Japanese market launch of “Cycloserine Capsules Meiji”)	<Applicable microorganisms> Cycloserine-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
k.	Streptomycin sulfate	July 1950 (Japanese market launch of "Streptomycin Meiji Sulfate”)	<Applicable microorganisms> Streptomycin-susceptible strains of genus *Mycobacterium*, *Yersinia pestis*, *Francisella tularensis*, genus *Leptospira* (Weil's disease) <Applicable conditions> Infective endocarditis (limited to cases of concomitant use with

	Non-proprietary name	Japanese market launch	Indications
			benzylpenicillin or ampicillin), plague, tularaemia, pulmonary tuberculosis and other tuberculosis, nontuberculous mycobacteriosis including MAC disease, Weil's disease
l.	Delamanid	September 2014	<Applicable microorganisms> Delamanid-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary multidrug-resistant tuberculosis
m.	Calcium paraaminosalicylate hydrate	April 1954	<Applicable microorganisms> Paraaminosalicylic acid-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
n.	Pyrazinamide	January 1956 (Japanese market launch of “Pyramide”)	<Applicable microorganisms> Pyrazinamide-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary tuberculosis and other tuberculosis
o.	Bedaquiline fumarate	May 2018	<Applicable microorganisms> Bedaquiline fumarate-susceptible strains of *Mycobacterium tuberculosis* <Applicable conditions> Pulmonary multidrug-resistant tuberculosis.
p.	Rifabutin	October 2008	<Applicable microorganisms> Rifabutin-susceptible strains of genus *Mycobacterium* <Applicable conditions> Tuberculosis, nontuberculous mycobacteriosis including MAC disease, prevention of onset of disseminated MAC disease in HIV-infected patients
q.	Rifampicin	August 1971 (Japanese market launch of “Rifadin Capsules”)	<Applicable microorganisms> Rifampicin-susceptible strains of genus *Mycobacterium* <Applicable conditions>

	Non-proprietary name	Japanese market launch	Indications
			Pulmonary tuberculosis and other tuberculosis, nontuberculous mycobacteriosis including MAC disease, leprosy
r.	Levofloxacin hydrate (oral dosage form)	July 2009	<Applicable microorganisms> Levofloxacin hydrate-susceptible strains of genus *Staphylococcus*, genus *Streptococcus*, *Pneumococcus*, genus *Enterococcus*, *Neisseria gonorrhoeae*, *Moraxella (Branhamella) catarrhalis*, *Bacillus anthrax*, *Mycobacterium tuberculosis*, *Escherichia coli*, *Shigella*, genus *Salmonella*, *Salmonella typhi*, *Salmonella enterica* serovar Paratyphi A, genus *Citrobacter*, genus *Klebsiella*, genus *Enterobacter*, genus *Serratia*, genus *Proteus*, *Morganella morganii*, genus *Providencia*, *Yersinia pestis*, *Vibrio cholerae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, genus *Acinetobacter*, genus *Legionella*, genus *Brucella*, *Francisella tularensis*, genus *Campylobacter*, genus *Peptostreptococcus*, *Propionibacterium acnes*, Q fever *Rickettsia* (*Coxiella burnetii*), *Chlamydia trachomatis*, *Chlamydia pneumonia*, *Mycoplasma pneumonia* <Applicable conditions> Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, acne (with suppurative inflammation), secondary infections following trauma, thermal burn, and surgical wound, mastitis, perianal abscess, pharyngitis/laryngitis, tonsillitis (including peritonsillitis, peritonsillar abscess), acute bronchitis, pneumonia, secondary infections of chronic respiratory lesions, cystitis, pyelonephritis, prostatitis (acute/chronic), epididymitis, urethritis, cervicitis, cholecystitis, cholangitis, infectious enteritis, typhoid, paratyphoid fever, cholera, bartholinitis, intrauterine infection, adnexitis, dacryocystitis, hordeolum, meibomianitis, otitis externa, otitis media, sinusitis, purulent sialoadenitis, periodontal inflammation, pericoronitis, jaw inflammation, anthrax, brucellosis, plague, tularaemia, pulmonary

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

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.

	Non-proprietary name	Japanese market launch	Indications
			tuberculosis and other tuberculosis, Q fever

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp