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Report on Investigation Results

March 2, 2018
Pharmaceuticals and Medical Devices Agency

I. Overview of drug

[Non-proprietary name]	Adrenaline
[Brand name]	As shown in Appendix 1
[Approval holder]	As shown in Appendix 1
[Indications	As shown in Appendix 1
[Dosage and Administration]	As shown in Appendix 1
[Notes]	Nothing in particular
[Investigating office]	Office of Safety II

II. Background of this investigation

1. Status of adrenaline preparations in Japan

Adrenaline acts on α- and β-adrenergic receptors in the sympathetic nervous system and shows sympathomimetic action. It increases heart rate, myocardial contractility, and cardiac output, and shows cardiotonic action in the heart (β1 stimulatory action). It also has vasoconstrictive action on the skin and mucous membranes (α1 stimulatory action), vasodilatory action on the skeletal muscles and viscera (including coronary arteries), relaxant action on the bronchial smooth muscle, and bronchodilator action (β2 stimulatory action).

Adrenaline is currently available in the following preparations:

- Adrenaline 1 mg/2 mL for injection and adrenaline 2 mg/2 mL for injection (hereinafter, "adrenaline preparations for emergency supplemental treatment of anaphylaxis") with the indications for emergency supplemental treatment of anaphylactic reactions caused by allergens in vespid venom, food and drugs[1] and other allergens
- Adrenaline 1 mg/1 mL for injection (hereinafter, "adrenaline preparations for emergency supplemental treatment of shock") with the indications for remission of bronchospasm of bronchial asthma and pertussis, emergency supplemental treatment of acute hypotension or shock associated with various diseases or conditions, emergency supplemental treatment of cardiac arrest, prolonged action of local anesthetics, prevention and treatment of local haemorrhage during surgery, and prevention of iris adhesions at the onset of iridocyclitis[2];
- Adrenaline 1 mg/1 mL (adrenaline preparations for topical application for treatment of remission of bronchospasm) with the indications for remission of bronchospasm of bronchial asthma and pertussis, prolonged action of local anesthesia (limited to surface anesthesia of mucosa), prevention and treatment of local haemorrhage during surgery, local haemorrhage in the field of otorhinolaryngology, mucosal hyperaemia/swelling, and local hemorrhage from a wound[3],
- Adrenaline 0.01 mg/1 mL and lidocaine hydrochloride 5 mg/1 mL injection, adrenaline 0.01 mg/1 mL and lidocaine hydrochloride 10 mg/1 mL injection, and adrenaline 0.0125 mg/mL and lidocaine hydrochloride 20 mg/1 mL injection (adrenaline preparations for anesthetic use) with the indications for epidural anesthesia, conduction anesthesia, and infiltration anesthesia[4],
- Adrenaline bitartrate 0.025 mg/1 mL and lidocaine hydrochloride 20 mg/1 mL for dental cartridge (adrenaline preparations for dental use) with the indications for infiltration anesthesia and conduction anesthesia in the field of dentistry[5].

2. Background that led to this investigation

A "written request for product labeling changes regarding Contraindications for Co-administration of adrenaline and antipsychotic agents with α-blocking actions" was submitted to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter, "Safety Division") by the Japanese Society of Allergology. Adrenaline is described as the first-line drug of the treatment of anaphylaxis in the "Guideline for Anaphylaxis First Version" (Japanese Society of Allergology; 2014); however, adrenaline is listed in the section of Contraindications for Co-administration in the package inserts of antipsychotic agents with α-blocking actions, including risperidone and aripiprazole. Considering

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1 Date of approval: Emergency supplemental of anaphylactic reaction due to vespid venom (August 1, 2003), emergency supplemental of anaphylactic reaction due to food and drug allergy (March 4, 2005)
2 Date of approval: June 26, 1997 (change of brand name)
3 Date of approval: June 26, 1997 (change of brand name)
4 Date of approval: February 1, 1956 (date of former approval)
5 Date of approval: June 29, 2009 (change of brand name)

that adrenaline injections, the first-line drug of the treatment of anaphylaxis, cannot be used at the onset of anaphylaxis in patients receiving the relevant antipsychotic agents, the Japanese Society of Allergology requested to remove the current description of contraindications for Co-administration of the adrenaline injections and antipsychotic agents with α-blocking actions. In response to this written request, the Safety Division requested the Pharmaceuticals and Medical Devices Agency (hereinafter, "PMDA") to conduct an "investigation regarding the safety related to administration of adrenaline preparations used for the emergency treatment of anaphylaxis in patients who are on antipsychotic agents with α-blocking actions" on February 14, 2018.

PMDA has held an Expert Discussion as part of the investigation. The expert advisors for the Expert Discussion were nominated based on their declarations, concerning the products, in accordance with the provisions of "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8 dated December 25, 2008).

III. Investigation by PMDA

Among adrenaline preparations, 'adrenaline preparations for emergency supplemental treatment of anaphylaxis' and 'adrenaline preparations for emergency supplemental treatment of shock' were investigated, because the package inserts of these two adrenaline preparations include the language of "Aantipsychotic agents with α-blocking actions including butyrophenones and phenothiazines, and α- blockers"[6] in the sections of "Contraindications and "Contraindications for Co-administration" and the description that the preparations are used for anaphylaxis.

1. Accumulation status of adverse reaction reports in Japan

A search of adverse reaction reports from the marketing authorization holders of the adrenaline preparations was performed to retrieve the relevant case for decreased blood pressure in patients receiving antipsychotic agents with α-blocking actions and/or α blockers concomitantly[7] (data lock point: January 18, 2018[8]).

There were 5 cases, including 1 case of haloperidol, 1 case of chlorpromazine hydrochloride/promethazine hydrochloride/phenobarbital combination product and levomepromazine maleate, 1 case of aripiprazole, 1 case of risperidone, and 1 case of risperidone and chlorpromazine hydrochloride as concomitant drugs (the term of the adverse reaction was "blood pressure decreased" and the outcome was "recovered/resolved" in all cases) (Appendix 2).

2. Accumulation status of descriptions in labels and adverse reaction reports in other countries

In the United States Product Information (USPI) and British Summary of Product Characteristics (SPC) of the adrenaline preparations, antipsychotic agents with α-blocking actions and α blockers are not contraindicated for co-administration, and it is described that adrenaline reversal may occur by concomitant use of these preparations and administration of another pressor drug such as levarterenol (not approved in Japan) may be necessary in the section related to interactions (Attachment).

[6] It was assumed pharmacologically that hypotension will occur due to adrenaline reversal because β-receptor stimulating action becomes dominant by concomitant use with a drug with α-blocking actions [Interview Form of adrenaline preparations for emergency supplemental treatments of shock (12th version)].

[7] Events that include "blood pressure decreased", "hypotension", and "blood pressure fluctuation" in the preferred term of the ICH Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) Ver. 20.1.

[8] The adrenaline preparations for emergency supplemental treatment of anaphylaxis were tabulated from the date of approval (August 1, 2003) and the adrenaline preparations for emergency supplemental treatment for shock were tabulated from April 1, 1997.

Furthermore, as a result of a search of adverse reaction reported in other countries, there were 5 reports including 3 cases of quetiapine fumarate, 1 case of carvedilol, and 1 case of clozapine (the names of adverse reactions were 2 cases of “blood pressure decreased”, 1 case of “blood pressure systolic decreased”, 1 case of "mean arterial pressure decreased” and 1 case of “blood pressure fluctuation”, and the outcome included 4 cases of “recovered/resolved” and 1 case of “unknown”) (Appendix 2).

3. Descriptions in textbooks and treatment guidelines in Japan and other countries

3.1. Textbooks

In standard textbooks of internal medicine, it is described that early response to anaphylaxis is essential since it results in death in several minutes to several hours from the initial symptoms and adrenaline should be injected subcutaneously or intramuscularly as the treatment in the Harrison's Principles of Internal Medicine 19th edition (McGraw-Hill Professional; 2015. p2116), and anaphylaxis is the most important allergic reaction that may result in death and requires urgent attention, and intramuscular injection of adrenaline is the first-line drug in the Goldman-Cecil Medicine 24th edition (Elsevier; 2012. p1613). In the standard textbook of pediatrics, it is described that anaphylaxis is a serious allergic reaction that progresses rapidly and results in death once it occurs, and intramuscular or intravenous injection of adrenaline is the first-line drug for treatment in the Nelson Textbook of Pediatrics 20th edition (Elsevier; 2015. p1131).

It is described that anaphylaxis is fatal and requires prompt response, and intramuscular or intravenous injection of adrenaline is one of the treatments that should be provided in the initial phase in the Guideline for Emergency Care Fourth Version (Herusu Shuppan; 2011. p586).

3.2 Guidelines

The Food Allergy and Anaphylaxis Guidelines[9] and the World Allergy Organization Guideline for the Assessment and Management of Anaphylaxis[10] by European Academy of Allergy & Clinical Immunology and the World Allergy Organization describes that intramuscular injection of adrenaline is the first-line treatment for anaphylaxis with no description of contraindications for co-administration with antipsychotic agents with α-blocking actions and α blockers, stating use of in-hospital emergency system at the medical institutions or requesting a support such as an ambulance outside the medical institutions with use of adrenaline preparations to allow responses to a sudden change of patient’s condition as the basic treatment procedure. In Japan, Guideline for Anaphylaxis First Version by the Japanese Society of Allergology also describes that intramuscular injection of adrenaline is the first-line treatment and support of the emergency medical services in community setting system including an ambulance should be requested after administration. Moreover, the Japanese Pediatric Guideline for Food Allergy 2016 (Kyowa Kikaku; 2016. p141) by the Japanese Society of Pediatric and Clinical Immunology describes that intramuscular injection of adrenaline is the first-line treatment for anaphylaxis, and use of adrenaline for the purpose of saving the patient's life at the discretion of the physician should be acceptable when a patient taking these antipsychotic agents developed anaphylaxis although antipsychotic agents with α-blocking actions and adrenaline preparations are contraindicated for co-administration in the package inserts.

4. Literature

[9] http://www.eaaci.org/foodallergyandanaphylaxisguidelines/Food%20Allergy%20-%20web%20version.pdf
[10] World Allergy Organization J, 2011; 4:13-37

Of the research reports and action reports submitted to PMDA by January 18, 2018, there was no report related to co-administration with antipsychotic agents with α-blocking actions or α blockers.

A prescription survey of adrenaline was conducted by the committees on pharmaceutical affairs by the Japanese Society of Psychosomatic Pediatrics and the Japanese Society of Pediatric Psychiatry and Neurology. Medical records between September 2011 and March 2017 at 3 hospitals were reviewed. There were 7 cases of co-administration by overlapped prescription of an adrenaline preparation and risperidone or aripiprazole, however, there was no report of decreased blood pressure that is considered to be due to the co-administration[11].

IV. PMDA's conclusion based on the investigation results

Anaphylaxis is a fatal condition that requires prompt emergency treatment. Therefore use of adrenaline preparations for anaphylaxis under the system enabling responses to a sudden change of the patient's condition is considered to be acceptable even though the risk of decreased blood pressure induced by adrenaline reversal is taken into account. There is no report of a serious outcome in the information on adverse reactions accumulated in Japan, and α blockers are not contraindicated for co-administration in the drug labeling (USPI, British SPC etc.) of adrenaline in other countries.

In view of above, PMDA concluded that "adrenaline preparations for emergency supplemental treatment of anaphylaxis" and "adrenaline preparations for emergency supplemental treatment of shock" can be used in patients who are on antipsychotic agents with α-blocking actions and α blockers only when anaphylaxis or anaphylactic shock occurred.

Additionally, PMDA determined it appropriate to revise the package inserts of the adrenaline preparations as follows.

- For the adrenaline preparations for emergency supplemental treatment of anaphylaxis, the description of "Antipsychotic agents with α-blocking actions including butyrophenones and phenothiazines, and α-blockers" in the sections of Contraindications and Contraindications for Co-administration shall be deleted and co-administration with the relevant drugs should be listed in the section of Precautions for Co-administration to call attention.
- For the adrenaline preparations for emergency supplemental treatment of shock, the description that "except when used for the emergency treatment of anaphylactic shock" should be added to "Antipsychotic agents with α-blocking actions including butyrophenones and phenothiazines, and α-blockers" in the section of Contraindications and Contraindications for Co-administration to allow its use for patients on antipsychotic agents with α-blocking actions and α blockers.

For antipsychotic agents with α-blocking actions that are contraindicated for co-administration with adrenaline (Reference), PMDA also determined it appropriate to add the description that "(except when adrenaline is used for the emergency treatment of anaphylaxis)" in the descriptions related to adrenaline in the sections of Contraindications and Contraindications for Co-administration in association with the revision of the package inserts of the above adrenaline preparations.

[11] "Committee on pharmaceutical affairs - Preliminary survey on prescriptions and concomitant use of adrenaline preparations and risperidone or aripiprazole -" Journal of Japanese Society of Psychosomatic Pediatrics 2017; 26: 296-8

The expert advisers supported this with the opinion that the above PMDA's conclusion is clinically meaningful and appropriate even if there is the risk of decreased blood pressure based on the fact that anaphylaxis may be fatal.

V. Overall assessment

PMDA determined it appropriate to revise the "Precautions" of the package inserts as follow.

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[Proposed revision]Adrenaline (EpiPen Injection 0.15%, 0.3%)

Underlined language added, struck-out language deleted

<table>
<tr><th>Current version</th><th>Proposed revision</th></tr>
<tr><td>~~[CONTRAINDICATIONS]~~
~~Patients receiving the following agents [Refer to the section of "Contraindications for Co-administration"] Antipsychotic agents with α-blocking actions including butyrophenones and phenothiazines, and α-blockers~~</td><td>(Not described)</td></tr>
<tr><td>3. Interactions
(1)Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>~~Antipsychotic agents~~
~~Butyrophenones~~
~~Serenace~~
~~Tolopelon, etc.~~
~~Phenothiazines~~
~~Wintermin, etc.~~
~~Iminodibenzyls~~
~~Defekton, etc.~~
~~Zotepine~~
~~Lodopin~~
~~Risperidone~~
~~Risperdal~~</td><td>~~Hypotension may occur caused by adrenaline reversal of this drug.~~</td><td>~~Beta-stimulatory action of this drug is considered to become dominant due to the α-blocking actions of these drugs.~~</td></tr>
</table></td><td>3. Interactions
(1)Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>No related description</td><td>No related description</td><td>No related description</td></tr>
</table></td></tr>
</table>

~~α blockers~~		

(2)Precautions for Co-administration (This drug should be administered with care when co-administered with the following drugs.)

Name of drug	Clinical symptoms and measures	Mechanism and Risk Factors
No related description	No related description	No related description

(2)Precautions for Co-administration (This drug should be administered with care when co-administered with the following drugs.)

Name of drug	Clinical symptoms and measures	Mechanism and Risk Factors
Antipsychotic agents Butyrophenones Serenace Tolopelon, etc. Phenothiazines Wintermin, etc. Iminodibenzyls Defekton, etc. Zotepine Lodopin Risperidone Risperdal α blockers	Hypotension may occur due to adrenaline reversal.	Beta-stimulatory action of this drug is considered to become dominant due to the α-blocking actions of these drugs.

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[Proposed revision] Adrenaline (Bosmin Injection 1%)

Underlined language added, struck-out language deleted

<table>
<tr><th>Current version</th><th>Proposed revision</th></tr>
<tr><td>[Contraindications]
1. Patients receiving the following drugs (Refer to the section of “Interactions”)
(1) Antipsychotic agents with α-blocking actions including butyrophenones and phenothiazines, and α-blockers
(2) Omitted</td><td>[Contraindications]
1. Patients receiving the following drugs (Refer to the section of “Interactions”)
(1) Antipsychotic agents with α-blocking actions including butyrophenones and phenothiazines, and α-blockers (except when used for the emergency treatment of anaphylactic shock.)
(2) Omitted</td></tr>
<tr><td>2. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Antipsychotic agents
Butyrophenones
(Serenace, Tolopelon, etc.)
Phenothiazines
(Wintermin, etc.)
Iminodibenzyls
(Defecton, etc.)
Zotepine
(Lodopin)
Risperidone
(Risperdal)
α blockers</td><td>Hypotension may occur due to adrenaline reversal.</td><td>Omitted</td></tr>
</table></td><td>2. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Antipsychotic agents
Butyrophenones
(Serenace, Tolopelon, etc.)
Phenothiazines
(Wintermin, etc.)
Iminodibenzyls
(Defecton, etc.)
Zotepine
(Lodopin)
Risperidone
(Risperdal)
α blockers</td><td>Hypotension may occur due to adrenaline reversal. Adrenaline should not be co-administered except when used for the emergency treatment of anaphylactic shock.</td><td>Omitted</td></tr>
</table></td></tr>
</table>

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[Proposed revision]Asenapine maleate, aripiprazole, olanzapine, quetiapine fumarate, clocapramine hydrochloride hydrate, chlorpromazine hydrochloride, chlorpromazine phenolphthalinate, chlorpromazine hydrochloride/promethazine hydrochloride/phenobarbital, spiperone, zotepine, timiperone, haloperidol, paliperidone, pipamperone hydrochloride, fluphenazine decanoate, fluphenazine maleate, brexpiprazole, bromperidol, prochlorperazine mesilate, prochlorperazine maleate, propericiazine, perphenazine, perphenazine fendizoate, perphenazine maleate, perphenazine hydrochloride, perospirone hydrochloride hydrate, mosapramine hydrochloride, risperidone (oral drug), levomepromazine maleate, levomepromazine hydrochloride

Underlined language added

<table>
<tr><th>Current version</th><th>Proposed revision</th></tr>
<tr><td>[Contraindications]
Patients receiving adrenaline (Refer to the section of “Interactions.”)</td><td>[Contraindications]
Patients receiving adrenaline <u>(except when adrenaline is used for the emergency treatment of anaphylaxis)</u> (Refer to the section of “Interactions.”)</td></tr>
<tr><td>[Precautions]
(3) Interactions
1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenaline
(Bosmin)</td><td>Omitted</td><td>Omitted</td></tr>
</table></td><td>[Precautions]
(3) Interactions
1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenaline
<u>(except when used for the emergency treatment of anaphylaxis)</u>
(Bosmin)</td><td>Omitted</td><td>Omitted</td></tr>
</table></td></tr>
</table>

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[Proposed revision]Aripiprazole hydrate, haloperidol decanoate, paliperidone palmitate, risperidone (injections)

Underlined language added

<table>
<tr><th>Current version</th><th></th><th>Proposed revision</th></tr>
<tr><td>[Contraindications]
Patients receiving adrenaline and/or clozapine (Refer to the section of “Interactions.”)</td><td></td><td>[Contraindications]
Patients receiving adrenaline (except when adrenaline is used for the emergency treatment of anaphylaxis) and/or clozapine (Refer to the section of “Interactions.”)</td></tr>
<tr><td>[Precautions]
3. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenaline (Bosmin)</td><td>Omitted</td><td>Omitted</td></tr>
</table></td><td></td><td>[Precautions]
3. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenaline (except when used for the emergency treatment of anaphylaxis) (Bosmin)</td><td>Omitted</td><td>Omitted</td></tr>
</table></td></tr>
</table>

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[Proposed revision]Clozapine

Underlined language added

<table>
<tr><th>Current version</th><th>Proposed revision</th></tr>
<tr><td>[Contraindications]
Patients receiving adrenergic agonists (adrenaline, noradrenaline) (Refer to the section of “Interactions.”)</td><td>[Contraindications]
Patients receiving adrenergic agonists (adrenaline, noradrenaline) <u>(except when adrenaline is used for the emergency treatment of anaphylaxis)</u> (Refer to the section of “Interactions.”)</td></tr>
<tr><td>[Precautions]
3. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenergic agonists
Adrenaline
(Bosmin)
Noradrenaline
(Noradrenaline)</td><td>Omitted</td><td>Omitted</td></tr>
</table></td><td>[Precautions]
3. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenergic agonists
Adrenaline
<u>(except when used for the emergency treatment of anaphylaxis)</u>
(Bosmin)
Noradrenaline
(Noradrenaline)</td><td>Omitted</td><td>Omitted</td></tr>
</table></td></tr>
</table>

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[Proposed revision]Blonanserin

Underlined language added

<table>
<tr><th>Current version</th><th>Proposed revision</th></tr>
<tr><td>[Contraindications]
(1) to (2) omitted
(3) Patients receiving adrenaline, azole antifungals (itraconazole, voriconazole, miconazole, fluconazole, fosfluconazole), HIV protease inhibitors (ritonavir, indinavir, lopinavir/ritonavir combination product, nelfinavir, saquinavir, darunavir, atazanavir, fosamprenavir), telaprevir or cobicistat (Refer to the section of “Interactions.”)
(4) Omitted</td><td>[Contraindications]
(1) to (2) omitted
(3) Adrenaline <u>(except when adrenaline is used for the emergency treatment of anaphylaxis) (Refer to the section of “Interactions.”)</u>
(4) Patients receiving azole antifungals (itraconazole, voriconazole, miconazole, fluconazole, fosfluconazole), HIV protease inhibitors (ritonavir, indinavir, lopinavir/ritonavir combination product, nelfinavir, saquinavir, darunavir, atazanavir, fosamprenavir), telaprevir or cobicistat (Refer to the section of “Interactions.”)
<u>(5) Omitted As described in (4) of the current version</u></td></tr>
<tr><td>[Precautions]
3. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenaline (Bosmin)</td><td>Omitted</td><td>Omitted</td></tr>
</table>
</td><td>[Precautions]
3. Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs.)
<table>
<tr><th>Name of drug</th><th>Clinical symptoms and measures</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Adrenaline <u>(except when used for the emergency treatment of anaphylaxis)</u> (Bosmin)</td><td>Omitted</td><td>Omitted</td></tr>
</table>
</td></tr>
</table>

Appendix 1

Non-proprietary name	Brand name	Approval holder	Ingredient/Content	Indications	DOSAGE AND ADMINISTRATION
Adrenaline	EpiPen Injection 0.15 mg, EpiPen Injection 0.3 mg	Mylan EPD G.K.	Adrenaline 1 mg/2 mL, Adrenaline 2 mg/2 mL	Emergency supplemental treatment of anaphylactic reaction caused by vespid venom, food and drugs and other allergens (limited to patients with a history of anaphylaxis or at increased risk of developing anaphylaxis)	Usually, 0.01 mg/kg of adrenaline is the recommended dose, and 0.15 mg or 0.3 mg of adrenaline should be administered as intramuscular injection in consideration of the patient's body weight.
	Bosmin Injection 1 mg, others	Daiichi Sankyo Company, Limited, others	Adrenaline 1 mg/1 mL	Remission of bronchospasm based on the following diseases Asthma bronchial, pertussis ・ Emergency supplemental treatment of acute hypotension or shock associated with diseases and conditions ・ Prolonged action of local anesthetics ・ Prevention and treatment of local hemorrhage during surgery ・ Emergency supplemental treatment of cardiac arrest ・ Prevention of iris adhesions at the onset of iridocyclitis	[Remission of bronchospasm based on asthma bronchial and pertussis, emergency supplemental treatment of acute hypotension or shock associated with diseases and conditions, emergency supplemental treatment of cardiac arrest] The usual adult dose of adrenaline is 0.2 to 1 mg (0.2 to 1 mL) by subcutaneous or intramuscular injection. The dose should be adjusted based on the patient's age and symptoms. In the event of an emergency such as resuscitation, the usual dose of adrenaline not exceeding 0.25 mg (0.25 mL) should be diluted with saline and administered as intravenous infusion as slowly as possible. Repeat on 5- to 15-minute

					intervals whenever necessary. [Prolonged action of local anesthetics] As 0.1% adrenaline solution, 1 to 2 drops (adrenaline concentration 1: 100 000 to 200 000) should be added to a vasoconstrictor-free local anesthetic 10 mL before use. The dose should be adjusted based on the patient's age and symptoms. [Prevention and treatment of local hemorrhage during surgery] As 0.1% adrenaline solution, it should be administered solely or added to a local anesthetic and administered as a local injection. The dose should be adjusted based on the patient's age and symptoms. [Prevention of iris adhesions at the onset of iridocyclitis] As 0.1% adrenaline solution, it should be instilled in the eye or a dose below 0.1 mg (0.1 mL) should be injected subconjunctivally. The dose should be adjusted based on the patient's age and symptoms.

Appendix 2

Accumulation status of adverse reactions in Japan

No.	Age	Sex	PT for adverse reactions	Concomitant use of antipsychotic agents and drugs with α blocking actions	Seriousness	Outcome	Reason for use of adrenaline
1	Eighties	Male	Blood pressure decreased	Haloperidol	Serious	Recovered	Spinal anesthesia
2	Sixties	Female	Blood pressure decreased	Chlorpromazine hydrochloride/promethazine hydrochloride/phenobarbital combination product, Levomepromazine maleate	Serious	Recovered	Hypotension
3	Twenties	Male	Blood pressure decreased	Risperidone	Non-serious	Recovered	Local anesthesia
4	Thirties	Male	Blood pressure decreased	Risperidone, Chlorpromazine hydrochloride	Non-serious	Recovered	Local anesthesia
5	Seventies	Female	Blood pressure decreased	Aripiprazole	Serious	Recovered	Lumbar spinal stenosis

Accumulation status of adverse reactions in other countries

No.	Age	Sex	PT for adverse reactions	Concomitant use of antipsychotic agents and drugs with α blocking actions	Seriousness	Outcome	Reason for use of adrenaline
1	Fifties	Female	Blood pressure decreased	Quetiapine fumarate	Serious	Recovered	Hypotension
2	Thirties	Male	Blood pressure decreased	Quetiapine fumarate	Non-serious	Recovered	Hypotension
3	Twenties	Male	Blood pressure systolic decreased	Quetiapine fumarate	Serious	Recovered	Hypotension
4	Thirties	Male	Blood pressure fluctuation	Carvedilol	Serious	Unknown	Unknown
5	Fifties	Male	Mean arterial pressure decreased	Clozapine	Non-serious	Recovered	Blood pressure increased

References

Antipsychotic agents with α-blocking actions for which adrenaline is contraindicated

Non-proprietary name	Brand name	Approval holder
Asenapine Maleate	Sycrest Sublingual Tablets 5 mg, 10 mg	Meiji Seika Pharma Co., Ltd.
Aripiprazole hydrate	Abilify Prolonged Release Aqueous Suspension for IM Injection 300 mg, 400 mg, 300 mg Syringe, 400 mg Syringe	Otsuka Pharmaceutical Co., Ltd.
Aripiprazole	Abilify Tablets 1 mg, 3 mg, 6 mg, 12 mg, Abilify Powder 1%, Abilify OD Tablets 3 mg, 6 mg, 12 mg, 24 mg, Abilify Oral Solution 0.1%, others	Otsuka Pharmaceutical Co., Ltd., others
Olanzapine (Injection)	Zyprexa Intra-Muscular Injection 10 mg	Eli Lilly Japan K.K.
Olanzapine (oral)	Zyprexa Tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Zydis Tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granules 1%, others	Eli Lilly Japan K.K., others
Quetiapine fumarate	Seroquel Tablets 25 mg, 100 mg, 200 mg, Seroquel Fine Granules 50%, others	Astellas Pharma Inc., others
	Bipresso Extended Release Tablets 50 mg, 150 mg	Astellas Pharma Inc.
Clocapramine hydrochloride hydrate	Clofekton Tablets 10 mg, 25 mg, 50 mg	Zensei Pharmaceutical Industries Co., Ltd.
	Clofekton Granules 10%, others	Mitsubishi Tanabe Pharma Corporation, others
Clozapine	Clozaril Tablets 25 mg, 100 mg	Novartis Pharma K.K.
Chlorpromazine hydrochloride (Injection)	Contomin Intramuscular Injection 10 mg, 25 mg, 50 mg	Mitsubishi Tanabe Pharma Corporation
Chlorpromazine hydrochloride (Oral)	Contomin Sugar-Coated Tablets 12.5 mg, 25 mg, 50 mg, 100 mg	Mitsubishi Tanabe Pharma Corporation
	Chlorpromazine Hydrochloride Tablets 25 mg “Tsuruhara”	Tsuruhara Pharmaceutical Co., Ltd.
Chlorpromazine phenolphthalinate	Wintermin Fine Granules (10%)	Shionogi & Co., Ltd.

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Non-proprietary name	Brand name	Approval holder
Chlorpromazine hydrochloride/promethazine hydrochloride/phenobarbital	Vegetamin-A Combination Tablets, Vegetamin-B Combination Tablets	Shionogi & Co., Ltd.
Spiperone	Spiropitan Tablets 0.25 mg, 1 mg	Sannova Co., Ltd.
Zotepine	Lodopin Tablets 25 mg, 50 mg, 100 mg, Lodopin Fine Granules 10%, 50%, others	Astellas Pharma Inc., others
Timiperone (Injection)	Tolopelon Injection 4 mg	Daiichi Sankyo Company, Limited
Timiperone (Oral)	Tolopelon Tablets 0.5 mg, 1 mg, 3 mg, Tolopelon Fine Granules 1%, others	Daiichi Sankyo Company, Limited, others
Haloperidol (Injection)	Serenace Injection 5 mg, others	Sumitomo Dainippon Pharma Co., Ltd., others
Haloperidol (Oral)	Serenace Tablets 0.75 mg, 1 mg, 1.5 mg, 3 mg, Serenace Fine Granules 1%, Serenace Oral Solution 0.2%, others	Sumitomo Dainippon Pharma Co., Ltd., others
Haloperidol decanoate	Halomonth Injection 50 mg, 100 mg	Janssen Pharmaceutical K.K.
	Neoperidol Injection 50, 100	Johnson & Johnson K.K.
Paliperidone	Invega Tablets 3 mg, 6 mg, 9 mg	Janssen Pharmaceutical K.K.
Paliperidone palmitate	Xeplion Aqueous Suspension for IM Injection 25 mg Syringe, 50 mg Syringe, 75 mg Syringe, 100 mg Syringe, 150 mg Syringe	Janssen Pharmaceutical K.K.
Pipamperone hydrochloride	Propitan Tablets 50 mg, Propitan Powder 10%	Sannova Co., Ltd.
Fluphenazine decanoate	Fludecasin Intramuscular Injection 25 mg	Mitsubishi Tanabe Pharma Corporation
Fluphenazine maleate	Flumezin Sugar-Coated Tablets (0.25), (0.5), (1), Flumezin Powder 0.2%	Mitsubishi Tanabe Pharma Corporation
Brexpiprazole	Rexulti Tablets 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.
Prochlorperazine mesilate	Novamin Intramuscular Injection 5 mg	Shionogi & Co., Ltd.
Prochlorperazine maleate	Novamin Tablets 5 mg	Shionogi & Co., Ltd.
Non-proprietary name	Brand name	Approval holder

Blonanserin	Lonasen Tablets 2 mg, 4 mg, 8 mg, Lonasen Powder 2%	Sumitomo Dainippon Pharma Co., Ltd.
Propericiazine	Neuleptil Tablets 5 mg, 10 mg, 25 mg, Neuleptil Fine Granules 10%, Neuleptil Oral Solution 1%	TAKATA Pharmaceutical Co., Ltd.
Bromperidol	Impromen Tablets 1 mg, 3 mg, 6 mg, Impromen Fine Granules 1%, others	Janssen Pharmaceutical K.K., others
Perphenazine hydrochloride	PZC Intramuscular Injection 2 mg	Mitsubishi Tanabe Pharma Corporation
Perphenazine	Trilafon Tablets 2 mg, 4 mg, 8 mg, Trilafon Powder 1%	Kyowa Pharmaceutical Industry Co., Ltd.
Perphenazine fendizoate	PZC Powder 1%	Mitsubishi Tanabe Pharma Corporation
Perphenazine maleate	PZC Sugar-Coated Tablets 2 mg, 4 mg, 8 mg	Mitsubishi Tanabe Pharma Corporation
Perospirone hydrochloride hydrate	Lullan Tablets 4 mg, 8 mg, 16 mg, others	Sumitomo Dainippon Pharma Co., Ltd., others
Mosapramine hydrochloride	Cremin Tablets 10 mg, 25 mg, 50 mg, Cremin Granules 10%	Mitsubishi Tanabe Pharma Corporation
Risperidone (Injection)	Risperdal Consta Intramuscular Injection 25 mg, 37.5 mg, 50 mg	Janssen Pharmaceutical K.K.
Risperidone (Oral)	Risperdal Tablets 1 mg, 2 mg, 3 mg, Risperdal Fine Granule 1%, Risperdal OD Tablets 0.5 mg, 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL, others	Janssen Pharmaceutical K.K., others
Levomepromazine hydrochloride	Hirnamin Intramuscular Injection 25 mg	Shionogi & Co., Ltd.
	Levotomin Intramuscular Injection 25 mg	Mitsubishi Tanabe Pharma Corporation
Levomepromazine maleate	Hirnamin Tablets (5 mg), (25 mg), (50 mg), Hirnamin Powder 50%, Hirnamin Fine Granules 10%, others	Shionogi & Co., Ltd., others
	Levotomin Tablets 5 mg, 25 mg, 50 mg, Levotomin Powder 10%, 50%, Levotomin Granules 10%, others	Mitsubishi Tanabe Pharma Corporation, others

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Status of the related descriptions in foreign package inserts (major antipsychotic agents with α-blocking actions)

Non-proprietary name	United States Package Insert (USPI) (February 2017)	European Summary of Product Characteristics (SPC) (October, 2017)
Aripiprazole	1 INDICATIONS AND USAGE ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indicated for the treatment of: ・ Schizophrenia ・ Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder ・ Adjunctive Treatment of Major Depressive Disorder ・ Irritability Associated with Autistic Disorder ・ Treatment of Tourette's disorder ABILIFY Injection is indicated for the treatment of: ・ Agitation associated with schizophrenia or bipolar mania	4.1 Therapeutic indications ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older. ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of new manic episodes in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.
	4 CONTRAINDICATIONS ABILIFY is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.	4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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Non-proprietary name	The United States Package Insert (USPI) (February 2017)	British Summary of Product Characteristics (SPC) (June 2015)
Risperidone	1 INDICATIONS AND USAGE 1.1 Schizophrenia RISPERDAL (risperidone) is indicated for the treatment of schizophrenia. Efficacy was established in 4 short-term trials in adults, 2 short-term trials in adolescents (ages 13 to 17 years), and one long-term maintenance trial in adults. 1.2 Bipolar Mania Monotherapy RISPERDAL is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in 2 short-term trials in adults and one short-term trial in children and adolescents (ages 10 to 17 years). Adjunctive Therapy RISPERDAL adjunctive therapy with lithium or valproate is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in one short-term trial in adults. 1.3 Irritability Associated with Autistic Disorder RISPERDAL is indicated for the treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Efficacy was established in 3 short-term trials in children and adolescents (ages 5 to 17 years).	4.1 Therapeutic indications RISPERDAL is indicated for the treatment of schizophrenia. RISPERDAL is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders. RISPERDAL is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. RISPERDAL is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians very familiar with the treatment of conduct disorder of children and adolescents.
	4 CONTRAINDICATIONS RISPERDAL is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the RISPERDAL formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone is a metabolite of risperidone.	4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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Attachment

Descriptions related to co-administration with α blockers and adrenaline reversal in adrenaline preparations (epinephrine) in foreign package inserts (excerpt)

U.S. USPI

	Drug Name	Active Ingredients	Indications and Usage	Contraindications	Drug Interactions
1)	ADRENACLICK (05/2016)	epinephrine	Adrenaclick® is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which includes bees, wasps, hornets, yellow jackets and fire ants), and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media), and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. Adrenaclick is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Adrenaclick is intended for immediate administration as emergency supportive therapy only and is not a replacement or substitute for immediate medical care.	None.	The vasoconstricting and hypertensive effects of epinephrine are antagonized by alphaadrenergic blocking drugs, such as phentolamine.
2)	ADRENALIN (08/2017)	epinephrine	Adrenalin® is available as a single-use 1 mL vial and a multiple-use 30 mL vial for intramuscular and subcutaneous use. Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from allergic reactions to insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exerciseinduced anaphylaxis.	None.	The vasoconstricting and hypertensive effects of epinephrine are antagonized by alphaadrenergic blocking drugs, such as phentolamine. Ergot alkaloids may reverse the pressor effects of epinephrine. Epinephrine should not be used to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.

3)	AUVI-Q （11/2017）	epinephrine	Auvi-Q® is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. Auvi-Q is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Auvi-Q is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical care.	None.	The vasoconstricting and hypertensive effects of epinephrine are antagonized by alphaadrenergic blocking drugs, such as phentolamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.
4)	EPINEPHRINE （05/2016）	epinephrine	1.1 Hypotension associated with Septic Shock Epinephrine Injection USP, 1 mg/mL (1:1000) is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. 1.2 Anaphylaxis Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from allergic reactions to insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. The signs and symptoms associated with anaphylaxis include flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with hypotension, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, airway swelling, laryngospasm, bronchospasm, pruritus, urticaria or angioedema, swelling of the eyelids, lips, and tongue. 1.3 Induction and Maintenance of Mydriasis during Intraocular Surgery Induction and maintenance of mydriasis during intraocular surgery.	None.	Drugs antagonizing pressor effects of epinephrine ・ α-blockers, such as phentolamine Epinephrine should not be used to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.
5)	EPIPEN (04/2017)	epinephrine	EpiPen and EpiPen Jr are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects	None.	The vasoconstricting and hypertensive effects of

			(e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen and EpiPen Jr are intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema. EpiPen and EpiPen Jr are intended for immediate administration as emergency supportive therapy only and are not a substitute for immediate medical care.		epinephrine are antagonized by alphaadrenergic blocking drugs, such as phentolamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.
6)	EPIPEN JR.(04/2017)	epinephrine	EpiPen and EpiPen Jr are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen and EpiPen Jr are intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema. EpiPen and EpiPen Jr are intended for immediate administration as emergency supportive therapy only and are not a substitute for	None.	The vasoconstricting and hypertensive effects of epinephrine are antagonized by alphaadrenergic blocking drugs, such as phentolamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.

			immediate medical care.		
7)	SYMJEPI (06/2017)	epinephrine	SYMJEPI contains epinephrine, a non-selective alpha and betaadrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis	None.	The vasoconstricting and hypertensive effects of epinephrine are antagonized by alphaadrenergic blocking drugs, such as phentolamine. Ergot alkaloids: may reverse the pressor effects of epinephrine.

UK SPC (UKPI)

	Name of the Medicinal Product	Active Ingredients	Therapeutic Indications	Contraindications	Interaction with Other Medicinal Products and Other Forms of Interaction
1)	Adrenaline (Epinephrine) Injection 1:10,000 (glass prefilled syringe) (07/2017)	adrenaline acid tartrate	Cardiopulmonary Resuscitation in adults children and newborn Acute anaphylaxis	These should be regarded as relative and not absolute contraindications in life threatening emergency situations Adrenaline is contraindicated in patients with shock (other than anaphylactic shock), organic heart disease, or cardiac dilatation, as well as most patients with arrhythmias, organic brain damage, or cerebral arteriosclerosis. Adrenaline injection is contraindicated in patients with narrow angle glaucoma. Adrenaline is contraindicated for use during general anaesthesia with chloroform, trichloroethylene, or cyclopropane, and should be used cautiously, it at all, with other halogenated hydrocarbon anaesthetics and adrenaline is contraindicated for use in fingers, toes, ears, nose or genitalia.	Alpha and beta blocking agents: The cardiac and bronchodilating effects of adrenaline are antagonised by β-adrenergic blocking drugs such as propranolol, and the vasoconstriction and hypertension caused by high doses of adrenaline are antagonised by alpha-adrenergic blocking agents such as phentolamine. Because of their alpha-adrenergic blocking properties, ergot alkaloids can reverse the pressor response to adrenaline Phenothiazine:Adrenaline should not be used to counteract circulatory collapse of hypotension caused by phenothiazines: a reversal of adrenaline's pressor effects resulting in further lowering of blood pressure may occur.

				Adrenaline should not be used during the second stage of labour (see pregnancy and lactation).	
2)	Adrenaline (Epinephrine) Injection BP 1 in 1000 (12/2017)	adrenaline acid tartrate	Adrenaline Injection BP 1 in 1000 may be used in the treatment of acute allergy and anaphylactic shock.	Hypersensitivity to adrenaline, sodium metabisulfite or any of the other ingredients. Adrenaline 1 in 1000 should not be used in fingers, toes, ears, nose or genitalia owing to the risk of ischaemic tissue necrosis.	Alpha-adrenergic blocking agents: Alpha-blockers such as phentolamine antagonise the vasoconstriction and hypertension effects of adrenaline. This effect may be beneficial in adrenaline overdose (See section 4.9). Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers such as guanethidine with the risk of severe hypertension.
3)	Adrenaline 1 mg/10 ml (1:10,000), solution for injection in pre-filled syringe (01/2018)	adrenaline tartrate	Cardiopulmonary resuscitation Acute anaphylaxis in adults	Patients with known hypersensitivity to an excipient, where an alternative presentation of adrenaline or alternative vasopressor is available.	Alpha-adrenergic blocking agents: Alpha-blockers antagonise the vasoconstriction and hypertension effects of adrenaline, increasing the risk of hypotension and tachycardia.
4)	Adrenaline Injection BP 1/1000 (1mg/1ml) (12/2015)	adrenaline acid tartrate	Adrenaline is a direct-acting sympathomimetic agent. Adrenaline may be used to provide rapid relief of severe hypersensitivity reaction to drugs and other allergens, and in the emergency treatment of anaphylactic shock	Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Adrenaline should not be used during labour or, with local anaesthesia of peripheral structures including digits and ear lobe. Use in the presence of ventricular fibrillation, cardiac dilatation, coronary insufficiency, organic brain disease or atherosclerosis, except in emergencies where the potential	Alpha-adrenergic blocking agents: Alpha-blockers such as phentolamine antagonise the vasoconstriction and hypertension effects of adrenaline. This effect may be beneficial in adrenaline overdose. (See section 4.9). Phenothiazines: Phenothiazines block alpha-adrenergic receptors. Adrenaline should not be used to counteract circulatory collapse or hypotension caused by phenothiazines; a reversal of the pressor effects of

				benefit clearly outweighs the risk. Use if solution is discoloured.	Adrenaline may result in further lowering of blood pressure.
5)	Dilute Adrenaline (Epinephrine) Injection 1:10,000 (ampoules) （01/2018）	adrenaline acid tartrate	Cardiopulmonary Resuscitation Acute Anaphylaxis when intramuscular route has been ineffective.	These should be regarded as relative and not absolute contraindications in life threatening emergency situations. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 Adrenaline is contraindicated in patients with shock (other than anaphylactic shock), organic heart disease, or cardiac dilatation, as well as most patients with arrhythmias, organic brain damage, or cerebral arteriosclerosis. Adrenaline injection is contraindicated in patients with narrow angle glaucoma. Adrenaline is contraindicated for use during general anaesthesia with chloroform, trichloroethylene, or cyclopropane, and should be used cautiously, if at all, with other halogenated hydrocarbon anaesthetics. Adrenaline is contraindicated for use in fingers, toes, ears, nose or genitalia. Adrenaline should not be used during the second stage of labour (see pregnancy and lactation)	Alpha-blockers antagonise the vasoconstriction and hypertension effects of adrenaline, increasing the risk of hypotension and tachycardia
6)	Emerade, 150 micrograms, solution for injection in	adrenaline tartrate, epinephrine bitartrate	Emerade is indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-	There are no absolute contraindications to the use of Emerade in an allergic emergency.	The administration of fast-acting vasodilators or α-blockers can counteract the effects of adrenaline on blood pressure. β-blockers can inhibit the stimulating effect of adrenaline.

	pre-filled pen (01/2017)		induced or idiopathic anaphylaxis.		
7)	EpiPen Adrenaline (Epinephrine) Auto-Injector 0.3mg (11/2017)	adrenaline	EpiPen® auto injectors are automatic injection devices containing adrenaline for allergic emergencies. The auto injectors should be used only by a person with a history or an acknowledged risk of an anaphylactic reaction. The auto injectors are indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhoea and abdominal cramps, involuntary voiding, wheezing, dyspnoea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema. For these reasons auto injectors should always be carried by such persons in situations of potential risks.Adrenaline is considered the first line drug of choice for allergic emergencies. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in medical literature.Adrenaline is considered the first line drug of choice for allergic emergencies. Adrenaline effectively	There are no known absolute contraindications to the use of EpiPen® auto injector during an allergic emergency. Clinical conditions where special precautions are advised and drug interactions are prescribed in sections 4.4 and 4.5	Pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug, such as levarterenol.

			reverses the symptoms of rhinitis, urticaria, bronchospasm and hypotension because it is a pharmacological antagonist to the effects of the chemical mediators on smooth muscles, blood vessels and other tissues. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in medical literature.		
8)	EpiPen Jr Adrenaline (Epinephrine) Auto-Injector 0.15mg (11/2017)	adrenaline	EpiPen® Jr.auto injectors are automatic injection devices containing adrenaline for allergic emergencies. The auto injector is intended for children at a body weight of 7.5-25 kg.The auto injectors should be used only by a person with a history or an acknowledged risk of an anaphylactic reaction. The auto injectors are indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhoea and abdominal cramps, involuntary voiding, wheezing, dyspnoea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema. For these reasons auto injectors should always be carried by such persons in situations of potential	There are no known absolute contraindications to the use of EpiPen® Jr. during an allergic emergency. Clinical conditions where special precautions are advised and drug interactions are prescribed in sections 4.4 and 4.5	Pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug, such as levarterenol.

			risks.Adrenaline is considered the first line drug of choice for allergic emergencies. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in medical literature.Adrenaline is considered the first line drug of choice for allergic emergencies. Adrenaline effectively reverses the symptoms of rhinitis, urticaria, bronchospasm and hypotension because it is a pharmacological antagonist to the effects of the chemical mediators on smooth muscles, blood vessels and other tissues. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in medical literature.		
9)	Jext 150 micrograms Solution for Injection in pre-filled pen（11/2016）	adrenaline tartrate	Jext is indicated in the emergency treatment of severe acute allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis.	There are no absolute contraindications to the use of Jext during an allergic emergency.	The alpha- and beta-stimulating effect can be inhibited by concomitant use of alpha- and beta-blocking drugs as well as parasympathomimetic drugs.