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

Report on Investigation Results

November 30, 2020

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	a. Sildenafil citrate
	b. Amiodarone hydrochloride
[Branded name]	a. Revatio Tablets 20 mg, Revatio OD Film 20 mg, Revatio Dry Syrup for Suspension 900 mg
	b. Ancaron Tablets 100 and the others
[Approval holder]	a. Pfizer Japan Inc.,
	b. Sanofi K.K., and the others
[Indications]	See Appendix I
[Dosage and administration]	See Appendix I
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Sildenafil citrate (hereinafter referred to as “sildenafil”) is available in 2 types of preparations: One is preparations indicated for pulmonary arterial hypertension (PAH) (hereinafter referred to as “sildenafil (PAH)”) and the other is preparations indicated for erectile dysfunction (hereinafter referred to as “sildenafil (ED)”). Amiodarone hydrochloride (hereinafter referred to as “amiodarone”) is available in oral preparations and injections.

A cautionary statement for the contraindication of co-administration between sildenafil and amiodarone in the oral dosage form (hereinafter referred to as “amiodarone (oral dosage form)”) has been included in the CONTRAINDICATIONS section and the Contraindications for Co-administration section in the respective package inserts. The background of the contraindications is as follows:

- Mild QT interval prolongation effects were identified in the clinical study[1] of vardenafil hydrochloride hydrate (hereinafter referred to as “vardenafil”), which is a phosphodiesterase 5 inhibitor (hereinafter “PDE5 inhibitor”). Based on the finding, it was determined that co-administration of this drug with Class III antiarrhythmic agents

[1] Evaluation of vardenafil and sildenafil on cardiac repolarization. Am J Cardiol 2004; 93: 1378-83

which possess strong QT interval prolongation effects should be contraindicated in the marketing authorization review process. Consequently, the language "Class III antiarrhythmic agents (such as amiodarone and sotalol)" was added to the CONTRAINDICATIONS section and Contraindications for Co-administration section of the package insert of vardenafil.[2]

- In response to the decision, vardenafil was added to the CONTRAINDICATIONS section as well as the Contraindications for Co-administration section of the package insert of admiodarone (oral dosage form). Sildenafil was also added to the CONTRAINDICATIONS section and the Contraindications for Co-administration section[3] based on the mild QT interval prolongation effects similar to that of vardenafil observed in the clinical study mentioned above[1] (PFSB 0323001 Attachment 2, dated March 23, 2007).
- In line with the above, amiodarone (oral dosage form) was added to the CONTRINDICATIONS section and Contraindications for Co-administration section of the package insert of sildenafil (ED). Similarly, amiodarone (oral dosage form) was added to the CONTRAINDICATIONS section and the Contraindications for Co-administration section of the package insert of sildenafil (PAH) which was under review for marketing authorization at that time.

On March 2, 2020, the Japanese Circulation Society (JCS) and the Japanese Society of Pediatric Cardiology and Cardiac Surgery submitted the Request concerning Lifting of Contraindication of Co-administration between Amiodarone Hydrochloride and Sildenafil Citrate (hereinafter the "request") to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter the "Pharmaceutical Safety Division"), based on the fact that pediatric indications of sildenafil are covered by health insurance and the wide use of the drug in the PAH population, as well as the expected necessity of co-administration of amiodarone (oral dosage form) when a PAH patient becomes complicated with serious tachycardia or a non-PAH patient develops supraventricular tachycardia following administration of sildenafil after Fontan procedure, for example. The Pharmaceutical Safety Division on March 19, 2020 requested that the

[2] Review report of vardenafil (April 23, 2004)https://www.pmda.go.jp/drugs/2004/P200400009/63000400_21600AMY00075_Q100_1.pdf
[3] For amiodarone (injections), based on the indications of the drug described as "the following life-threatening arrhythmia if they are refractory as well as requiring urgent treatment; ventricular fibrillation, ventricular tachycardia with unstable hemodynamics" and "Cardiac arrest due to cardioversion-resistant ventricular fibrillation or pulseless ventricular tachycardia," administration may be required in an emergency and relatively short term duration of treatment is expected. Consequently it was decided that similar level of precaution to the oral dosage form was not necessary. As a result, sildenafil was added to the Precaution for Co-administration section.

Pharmaceuticals and Medical Devices Agency (hereinafter "PMDA") conduct Investigation on Safety in Co-administration of Amiodarone Hydrochloride (tablets only) and Sildenafil Citrate (only those indicated for pulmonary arterial hypertension). PMDA conducted the investigation accordingly and considered the necessity of revision of the package insert.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion 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).

III. Summary of the data submitted by the marketing authorization holder

Cases involving prolonged QT Interval of sildenafil (PAH) reported post-marketing

1-1. Japanese cases

The marketing authorization holder (MAH) of sildenafil explains as follows:

From the specified drug use-results survey (survey period: April 2008 to May 2014) results for sildenafil (PAH) used in adults, 7 events in 7 cases of adverse reactions deemed to involve prolonged QT interval were retrieved using MedDRA® SMQ "Torsade de pointes/QT prolongation (SMQ) " (broad and narrow) (Ver. 18.0) from a total of 3 304 cases surveyed. Reported events were syncope (3 events in 3 cases), ventricular tachycardia, electrocardiogram QT prolonged, loss of consciousness, and sudden death (1 event in 1 case, each). The events were non-serious for the 1 case of syncope and were serious for the other 6 cases. Outcomes were "death" in the 1 event of sudden death, "recovered" in 3 events (2 events of syncope, 1 event of loss of consciousness), and "resolving" in 3 events (ventricular tachycardia, prolonged electrocardiogram QT, syncope, 1 event, each). Regarding the causal relationship between sildenafil and the respective events, the occurrence of the events could be an effect of the underlying disease namely cardiac failure, as well as the concomitant drug(s) in 1 of the 2 cases of syncope (serious), while the other case was kept on sildenafil and was resolving, indicating an effect of underlying diseases such as congestive cardiac failure. In the case of ventricular tachycardia, dilated cardiomyopathy and coronary spastic angina in the patient's history as well as the concomitant drug(s) could have affected the occurrence of the events. The hypokalaemia due to the concomitant drug(s) could have affected the occurrence of the event in the case of prolonged electrocardiogram QT. With no details available, the possibility of a causal relationship with sildenafil is not clear for the remaining 3 cases.

From the specified drug use-results survey (survey period: underway from September

2017) results for sldenafil (PAH) used in pediatric patients, no cases of adverse reactions have been identified (as of May 2020) that were deemed to involve MedDRA® SMQ “Torsade de pointes/QT prolongation (SMQ)” (broad and narrow) (Ver. 23.0) among the 290 cases for which survey forms were retrieved and fixed.

In the database of adverse reactions occurring in Japan held by the MAH, 9 events in 9 cases have been identified as deemed to involve MedDRA® SMQ “Torsade de pointes/QT prolongation (SMQ) ” (broad and narrow) (Ver. 23.0) as of May 2020 among cases other than those mentioned above that derived from the specified drug use-results survey. Reported events were ventricular fibrillation, cardio-respiratory arrest, and syncope (2 events in 2 cases, each), cardiac arrest, sudden cardiac death, and multiple organ dysfunction syndrome (1 event in 1 case, each). The cases were all serious. The outcome was “death” in the ventricular fibrillation, cardio-respiratory arrest, sudden cardiac death, and multi organ dysfunction syndrome cases (1 case, each). Other outcomes were “recovered” in 1 case of cardiac fibrillation and “unknown” in 1 case each of cardio-respiratory arrest, syncope, and cardiac arrest. Regarding the causal relationship between sildenafil and the events, arrhythmogenic right ventricular cardiomyopathy (ARVC) and J wave syndrome, the current conditions of the patient, as well as the concomitant drug(s) known for their risk of prolonged QT interval such as clarithromycin might have affected the sudden cardiac death case. With no details available, the causal relationship is not clear for the remaining cases.

No thorough QT studies have been performed so far.

1-2. Overseas cases

The MAH of sildenafil explains as follows:

The database of adverse events occurring overseas held by the MAH was searched using MedDRA® SMQ “Torsade de pointes/QT prolongation (SMQ)” (broad and narrow) (Ver. 23.0), and 18 adverse events by sildenafil in 15 cases were identified as deemed to involve prolonged QT interval (as of May 2020). Reported events were cardiac arrest (5 events in 5 cases), syncope (3 events in 3 cases), ventricular tachycardia, multi organ dysfunction syndrome (2 events in 2 cases, each), and prolonged electrocardiogram QT interval, ventricular fibrillation, cardiac fibrillation, cardio-respiratory arrest, loss of consciousness, and sudden death (1 event in 1 case, each). The cases were all serious. Outcomes were “death” in 4 events of cardiac arrest, 1 event of cardio-respiratory arrest, and 2 events of multi organ dysfunction syndrome, “not recovered” in 1 event of syncope, “resolving” in 1 event of ventricular fibrillation, “recovered” in 2 events of ventricular tachycardia and 1 event each

of cardiac arrest, loss of consciousness, sudden death, syncope, ventricular fibrillation, and "unknown" in 1 event each of prolonged electrocardiogram QT interval and syncope. The causal relationship between sildenafil and these events is considered as follows: In the 1 case of prolonged electrocardiogram QT interval, concomitant drugs were identified that could have contributed to the occurrence of the event (such as sertraline hydrochloride). The case developed chest pain and was administered amiodarone. Then on an unknown day, prolonged electrocardiogram QT interval developed. The causal relationship between sildenafil and prolonged electrocardiogram is not clear. In the 2 cases of syncope and 1 case of loss of consciousness, with no data on electrocardiogram available, the causal relationship between sildenafil and prolonged electrocardiogram QT interval is not clear. In all other cases, a temporal association between sildenafil administration and the event is found. However, the primary disease (PAH) or comorbidities such as hypotension might have affected the occurrence of the event. With no details available, the causal relationship between sildenafil and events is not clear in these cases.

2. Post-marketing experience with the co-administration of sildenafil and amiodarone

2-1. Japanese cases

The MAH of sildenafil explains as follows:

In the specified drug use-results survey of sildenafil (PAH) in adults (April 2008 to May 2014), amiodarone was co-administered in 24 among the total of 3 304 cases. The route of administration of amiodarone in these cases was oral only in 21 cases, intravenous only in 2 cases, and oral and intravenous in 1 case. The incidence of adverse drug reactions was 13.6% (447/3 280 cases) in patients without co-administration of amiodarone and 4.2% (1/24 patients) in patients with co-administration of amiodarone. In the only case of adverse reaction observed in association with co-administration of amiodarone, the event was non-serious hypotension, and the outcome was "resolving." In this case, amiodarone (oral dosage form) had been initiated prior to sildenafil, and the decreased blood pressure occurred 1 year and 6 months after the termination of amiodarone administration. Thus, the causal relationship between the adverse reaction and co-administration of sildenafil and amiodarone is not clear.

In the specified drug use-results survey of sildenafil (PAH) in pediatric patients, none of the 290 cases for which survey forms were retrieved and fixed were co-administered amiodarone (as of May 2020).

5 cases of co-administration of sildenafil (PAH) and amiodarone have been reported in Japan outside the above-mentioned specified drug use-results survey. None of the cases

reported development of any adverse reactions (as of May 2020).

2-2. Overseas cases

The MAH of sildenafil explains as follows:

Cases of co-administration of sildenafil (PAH) and amiodarone were retrieved from the overseas adverse drug reaction database held by the MAH and 303 events in 94 cases were identified (as of May 2020). Of these, 61 cases were serious and 33 cases were non-serious. The most common events (5 or more) were: Product use in unapproved indication (18 events), congestive cardiac failure, headache (10 events each), product use issue, malaise (8 events each), hypotension (7 events), off-label use, dyspnoea, cardiac failure (6 events, each), and pneumonia (5 events). Outcomes included “outcome death” (85 events), “not recovered” (70 events), “resolving” (30 events), “recovered” (41 events), “unknown” (77 events). Of the 94 cases, events deemed to involve MedDRA® SMQ “Torsade de pointes/QT prolongation (SMQ)” (broad and narrow) were identified in 5 cases, namely of cardiac arrest (3 events), loss of consciousness and multi organ dysfunction syndrome (1 event, each). The causal relationship between the co-administration of sildenafil and amiodarone and the events is considered as follows: No cases have been identified as indicating a causal relationship between the co-administration and the events. Of the 3 events of cardiac arrest in 3 cases, 2 events in 2 cases were associated with an underlying disease(s) or a concomitant drug(s) other than amiodarone that could be related to the event. No details are available for the remaining 1 case of 1 cardiac arrest and the causal relationship is not clear. The 1 case of 1 loss of consciousness was associated with an underlying disease(s) or a concomitant drug(s) other than amiodarone that could be related to the event. No details are available for the 1 case of 1 multi organ dysfunction syndrome and the causal relationship is not clear.

The evaluation of causality between the co-administration of sildenafil and amiodarone and the event in the other 89 cases is as follows. No cases have been identified as indicating a causal relationship between the co-administration and the event.

First, of the 72 cases in which amiodarone was reported as a “concomitant drug” among plural concomitant drugs, effects of an underlying disease(s) and a concomitant drug(s) other than amiodarone were suspected in 35 cases (with 3 events or more of congestive cardiac failure, product use in unapproved indication, cardiac failure, malaise, cardiac disorder, dizziness, dyspnoea, fall, product use issue, and pulmonary hypertension). Effects of a concomitant drug(s) other than amiodarone were suspected in 16 cases (with 3 events or more of product use in unapproved indication, product use issue, and prescribed

overdose). Effects exclusively by sildenafil were suspected in 8 cases in which events noted in the Precautions of the package insert for sldenafil (PAH) (including low back pain, and diarrhoea) had been reported. Patient mortalities were reported in 4 cases for which the causal relationship could not be evaluated in detail due to lack of sufficient information. Effects of an underlying disease(s) were suspected in 3 cases (of events including cerebrovascular accident). In 1 case of hypotension, a relationship to sildenafil was suspected but the causal relationship with the co-administration of amiodarone is not clear because of a lack of sufficient information. In the remaining 5 cases (of events including reduced visual acuity), the causal relationship is not clear due to lack of sufficient information.

Next, of the 7 cases in which amiodarone was reported as a “suspected concomitant drug” among the plural concomitant drugs, effects of a concomitant drug(s) other than amiodarone were suspected in 3 cases (of events including cerebrovascular disorder, and interstitial pneumonia). Effects of an underlying disease(s) and a concomitant drug(s) other than amiodarone were suspected in 2 cases (of events including tubulointerstitial nephritis). No details are available for the remaining 2 cases (of events including cardiac failure and cholestatic liver injury), and the causal relationship is not clear.

Lastly, among 4 cases for which amiodarone alone was reported as a “concomitant drug” or “suspected concomitant drug,” 1 case for which “drug interaction” was reported as the event, 1 case in which a medication(s) which could not be identified as a concomitant drug(s) was mentioned, 1 case for which off-label use to an infant was reported, and 3 cases for which only “off-label use,” “product use issue,” or “contraindicated product prescribed” was reported, 10 cases in total, effects of an underlying disease(s) or a concomitant drug(s) other than amiodarone were suspected in 1 case (of events including increased gamma-glutamyltransferase). With no details available, the causal relationship between the drug and events is not clear for the remaining 9 cases.

3. Description in published literature on the risk of prolonged QT interval with sildenafil

3-1. Statements of overseas package inserts

No statements concerning the risk of prolonged QT interval were found in the US and EU package inserts for sildenafil (PAH). In the Australian and Canadian package inserts that have been confirmed, no statements concerning the risk of prolonged QT interval were found either (see Appendix 3).

3-2. Published literature (clinical use)

The MAH of sildenafil explains as follows:

Embase, MEDLINE, and Ichushi web were searched for literature on clinical use of sildenafil with respect to the risk of prolonged QT interval (see Appendix 2-1 for conditions for search), and 1 clinical study was retrieved that indicates an involvement of sildenafil in prolonged QT interval. The study was the basis of the listing of "Class III antiarrhythmic agents (such as amiodarone and sotalol)" in the CONTRAINDICATIONS section and the Contraindication for Co-administration section of the package insert of vardenafil. Details of the study are as follows:

Single doses of vardenafil (10 and 80 mg), sildenafil (50 and 400 mg), moxifloxacin (400 mg), or a placebo were administered to 58 healthy adult males in a double-blinded crossover design, and 12-lead electrocardiograms (ECGs) were measured 3 time points (within 30 days, 30 minutes, and 15 minutes) before and 5 time points (30 minutes, 1 hour, 1.5 hours, 2.5 hours, and 4 hours) after dosing. The QTcF interval prolongation (point estimate (90% confidence interval)) was 6 (5-8) ms for sildenafil 50 mg, 9 (8-11) ms for 400 mg, and 8 (6-9) ms for moxifloxacin as a positive control. The absolute QT interval prolongation was -2 (-4-0) ms for sildenafil 50 mg, -1 (-3-1) ms for 400 mg, and 3 (1-5) ms for moxifloxacin.[1]

The MAH of sildenafil discusses as follows: Considering the trend observed in the study towards prolongation of QTcF interval by the administration of sildenafil at 50 mg and 400 mg, the possibility for sildenafil to prolong QT interval could not be ruled out.

Other literature that mentioned QT interval associated with sildenafil is summarized as follows:

- In 36 patients with erectile dysfunction, the maximum QTc values (mean ± standard deviation) were 437±24, 441±16, and 440±14 ms before, 1 hour, and 4 hours after administration of 50 mg sildenafil, respectively, and the minimum QTc values 401±21, 404±16, and 408±16 ms, respectively. There was no statistically significant difference in QTc before and after sildenafil administration[4].
- In a review article summarizing the safety of PDE5 inhibitors and their concomitant drugs, previous literature reports did not indicate that sildenafil and tadalafil caused a statistically significant change in QT interval[5].

[4] Sildenafil citrate does not affect QT intervals and QT dispersion: An important observation for drug safety. Ann Noninvasive Electrocardiol 2003; 8: 14-7
[5] The use of phosphodiesterase 5 inhibitors with concomitant medications. J Endocrinol Invest 2008; 31: 799-808

- The relevant guidelines developed on PDE5 inhibitors used for erectile dysfunction and cardiovascular risks state that no statistically significant QTc interval changes have been observed in sildenafil and tadalafil[6].

3-3. Published literature (non-clinical studies)

The MAH of sildenafil explains as follows:

For literature concerning non-clinical studies related to sildenafil and the risk of prolonged QT interval, studies that were assessed for the marketing authorization of sildenafil were reviewed and PubMed was searched for human ether-a-go-go-related gene (hERG) channel which is presumed to be a K+ channel subunit to form the rapid element (Ikr) of the delayed rectifier K+ channels (IK) of cardiomyocytes. As a result of the search, the only 1 study report in which sildenafil was associated with QT interval prolongation indicated that sildenafil further increased the pinacidil (ATP-sensitive K+ channel opener)-induced augmentation of cardiac Na^+/Ca^{2+} exchange current (INCX1)[7]. The study stated that the clinical significance of the increased augmentation was unknown at the time of the study.

Other literature indicated that no association was found between sildenafil and the risk of prolonged QT interval. Published literature on the risk of prolonged QT interval with sildenafil in non-clinical studies including data assessed in the marketing authorization review of sildenafil (ED) is summarized as follows:

- In a model where human ether-a-go-go-related gene (hERG) channels, which are known to be inhibited by drugs that cause QT interval prolongation, were forcedly expressed in human embryonic kidney cells, the concentration at which sildenafil affects hERG channels (IC_{50} 33 μM) deviated from the plasma concentration at clinical doses of sildenafil (C_{max} total to 0.843 μM)[8].
- Single doses of sildenafil 0.3, 1, or 3 mg/kg were orally administered to dogs and ECG measurement followed. The results indicated no changes suggesting that sildenafil produces direct effects on the cardiac conduction system[9].
- Sildenafil at doses of 0, 5, 20, or 80 mg/kg/day was orally administered to dogs for a month, and ECG revealed an increased P-wave amplitude and decreases in QT intervals in the 20 and 80 mg/kg/day groups[10].

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[6] Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 2005; 96(12B): 85M-93M
[7] Cardiac Na+/Ca2+ exchange stimulators among cardioprotective drugs. J Physiol Sci 2019; 69(6): 837-49
[8] Absence of clinical important HERG channel blockade by three compounds that inhibit phosphodiesterase 5 - sildenafil, tadalafil, and vardenafil. Eur J Pharmacol 2004; 502: 163-7
[9] Report Number HO-01-01:
Viagra™ (sildenafil citrate) NDA 5.B Nonclinical Pharmacology. Pfizer Central Research, Sandwich, Kent, U.K. CT13 9NJ
[10] Study Report 90125. 1-Month oral toxicity in dogs.

- Sildenafil at doses of 0, 3, 15, or 50 mg/kg/day were orally administered to dogs for 6 months, and ECGs were performed prior to the start of administration, and at weeks 6, 15, 23 of the study, and revealed decreases in QT intervals in the 15 and 50 mg/kg/day groups (-5% at 15 weeks and -10% at 23 weeks). Changes in the ECG of sinus arrhythmia, sinus arrest, transient atrioventricular block first or second degree, and extrasystoles or escaped beat were also observed in some dogs in each groups, but the onset was sporadic and the MAH of sildenafil determined that the changes were not attributable to administration[11].
- Sildenafil at doses of 0, 3, 10, or 50 mg/kg/day was orally administered to dogs for 12 months, and blood pressure and ECGs were measured prior to the start of administration, on days 12-14, 194-197, and 342-345. No changes in blood pressure were observed while increases in heart rate were observed in some groups. The MAH of sildenafil considered the increases in heart rate to have been caused by the compensatory changes in response to the vasodilatory properties of sildenafil. There was also a statistically significant increase in P-wave amplitude and decreases in PQ and QT intervals. The MAH of sildenafil determined that decreases in PQ and QT intervals were attributable to increases in heart rate[12] [13].

4. Description of published literature on the safety in co-administration of sildenafil and amiodarone

4-1. Statements of overseas package inserts

No statements concerning co-administration with amiodarone were found in the US, EU, Australian, and Canadian package inserts for sildenafil (PAH) (see Appendix 3).

The EU and Australian package inserts for amiodarone (oral dosage form) listed sildenafil as a CYP3A4 substrate in the Interactions with other Medicinal Products and Other Forms of Interaction section. No statements concerning co-administration of sildenafil were found in the US and Canadian package inserts for amiodarone (oral dosage form).

4-2. Statements in Japanese and overseas clinical practice guidelines

Japanese, US, and EU clinical practice guidelines for pulmonary hypertension or arrhythmia[14] were reviewed for statements concerning co-administration of sildenafil and

[11] Study Report 91099. 6-Month oral toxicity in dogs.
[12] Study Report 95039. 12-Month oral toxicity in dogs
[13] Electrocardiography, in Canine Cardiology. Saunders Company, Philadelphia 1970; 102-69
[14] The following clinical practice guidelines were confirmed:
- 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. Rev Esp Cardiol (Engl Ed). 2016

amiodarone, and no statements concerning the risk of the co-administration were identified.

4-3. Published literature

Japanese and overseas literature on the co-administration of sildenafil and amiodarone was searched and reviewed through Embase, MEDLINE, and Ichushi web (see Appendix 2-2 for conditions of search), and no descriptions indicating an increase of the risks induced by co-administration of sildenafil and amiodarone were identified.

III. Outline of Investigation by PMDA

1. Investigation on the necessity of co-administration of sildenafil (PAH) and amiodarone (oral dosage form)

Related US and EU clinical practice guidelines were reviewed for the situations that medically require sildenafil (PAH) and amiodarone (oral dosage form). The results of the review are as follows:

1.1 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2015 edition) (European Society of Cardiology and European Respiratory Society)[15]

Arrhythmias are an increasing clinical problem in PAH patients. In particular, the presence of symptomatic upper ventricular arrhythmia might portend a poor prognosis. Fatal ventricular arrhythmia is rare in PAH patients. Ventricular fibrillation was observed in 8% of a series of 132 cases of cardiac arrest witnessed in PAH patients. A study that performed a long-term follow-up of another series of 231 cases of patients with PAH or chronic thromboembolic pulmonary hypertension yielded an annual incidence of 2.8% for supraventricular tachycardia. Atrial flatter and atrial fibrillation were common and led to clinical deterioration

- 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016; 133: e506-74
- Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. 2015; 132: 2037-99
- 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circ Cardiovasc Qual Outcomes. 2016; 9: 443-88
- 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37: 2893-962
- 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019; 73: e81-e192
- 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019; 140: e125-e151

[15] Galiè N, et al. Rev Esp Cardiol (Engl Ed). 2016

with signs of right heart failure. Persistent atrial fibrillation was associated with 2-year mortality >80%, and a stable sinus rhythm was associated with a favorable long-term survival. These findings suggest that maintenance of a stable sinus rhythm after cardioversion should be considered an important treatment goal. In order to achieve a stable sinus rhythm, prophylaxis with antiarrhythmic drugs without negative inotropic effects such as oral amiodarone should be considered despite insufficient data on effectiveness.

1.2 ESC Guidelines for the management of grown-up congenital heart disease (new version 2010) (European Society of Cardiology)[16]

- Arrhythmias are the main reason for the hospitalization of grown-up congenital heart disease patients, and they are an increasingly frequent cause of morbidity and mortality.
- A large proportion of patients with congenital heart disease, in particular those with relevant systemic-to-pulmonary shunts, if left untreated, develop PAH. Among 1 877 patients with atrial septal defect, ventricular septal defect, or other cyanotic heart disease, 28% had pulmonary hypertension and 12% had Eisenmenger syndrome. In a more recent survey, of 1 824 patients with adult congenital heart disease patients with septal defects, 6.1% had PAH, and 3.5% had Eisenmenger syndrome.
- Endothelin receptor antagonists other than bosentan, PDE5 inhibitors, prostanoid should be considered in the WHO functional class IIIc patients with Eisenmenger syndrome (Class of recommendations IIa (Weight of evidence/opinion is in favor of usefulness/efficacy)).

1.3 PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease (2014 edition) (Partnership Between the Pediatric and Congenital Electrophysiology Society (PACE), Heart Rhythm Society)[17]

Amiodarone is the most effective antiarrhythmic agent for maintaining sinus rhythm in patients with atrial fibrillation and is the drug of choice in the setting of cardiac failure. However, long-term therapy is limited by time- and dose-dependent side effects (effects on the lungs, liver, thyroid, heart, etc.), particularly in young adults. While respecting precautions, amiodarone may be considered a first-line antiarrhythmic agent for the long-

[16] Baumgartner H, et al. Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). Eur Heart J. 2010; 31: 2915-57
[17] Khairy P, et al. Can J Cardiol. 2014 Oct;30(10):e1-e63

term maintenance of sinus rhythm in adults with congenital heart disease and intra-atrial reentrant tachycardia or atrial fibrillation in the presence of ventricular hypertrophy or dysfunction, or coronary artery disease.

Based on the above descriptions, PMDA considers there is a medical necessity of the co-administration of sildenafil (PAH) and amiodarone (oral dosage form) for the following reasons:

- Right heart failure is considered a factor that dictates the severity or prognosis of PAH (Guidelines for Treatment of Pulmonary Hypertension (2017 edition) (JCS, Japanese Pulmonary Circulation and Pulmonary Hypertension Society(JPCPHS)) and if patients with PAH accompanied by right heart failure concurrently develop tachycardia, amiodarone is to be considered an option for pharmacotherapy of tachycardia as a drug with weak cardiac function-suppressive effect (lacking negative inotropic action).
- Patients with congenital heart diseases may concurrently develop PAH, and management of tachycardia becomes crucial in these cases. Particularly in the PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease, amiodarone is stated as the first-line drug for the purpose of maintaining the sinus rhythm in patients with congenital heart diseases.
- Administration of amiodarone is required for the treatment following the acute phase, not only in its injectable, but also oral dosage forms.
- Sildenafil (PAH), unlike other PDE5 inhibitors, is the only PDE5 inhibitor that is indicated for pediatric use and has its pediatric preparations available. Therefore, no alternative drugs are available for the treatment of PAH in pediatric patients currently.

2. Investigation on the risk of prolonged QT intervals with sildenafil

The MAH of sildenafil explains the QT interval prolongation risk associated with sildenafil as follows:

No clear evidence has been identified for a QT interval prolongation risk posed by sildenafil in the specified drug use-results survey, other case reports in Japan, or case reports overseas.

Related clinical trials were in line with the statement of the ICH E14 Guidelines that “it appears that drugs associated with average QT/QTc interval prolongation of approximately 5 ms or less do not cause TdP. It is unknown whether this is because the risk posed by such drugs does not increase or the risk does increase but the increase is too small to be detected.”

The 1 clinical trial (see **3-2. Published literature (clinical use), 3. Description in published literature on the risk of prolonged QT interval with sildenafil, III. Summary of the data submitted by the marketing authorization holder**) which was the basis for the addition of class III antiarrhythmic agents to the contraindications for co-administration for vardenafil indicated that the risk of QT interval prolongation following administration of sildenafil is not clinically relevant; however, the risk itself could not be ruled out.

PMDA also reviewed case reports for cases involving QT Interval prolongation with sildenafil (ED). Among the 12 Japanese and 180 overseas (only those reported to PMDA) cases identified as involving MedDRA® SMQ "Torsade de pointes/QT prolongation (SMQ)" (broad and narrow) (Ver. 23.0), none clearly indicated a risk of prolonged QT interval by sildenafil (as of May 2020).

Taking account of the clinical study that supported the addition of class III antiarrhythmic agents to the contraindications for co-administration for vardenafil, PMDA considers the risk of prolonged QT interval following administration of sildenafil could not be ruled out.

3. Investigation on the necessity of co-administration of sildenafil (PAH) and amiodarone (oral dosage form)

The MAH of sildenafil explains the safety in the co-administration of sildenafil (PAH) and amiodarone (oral dosage form) as follows:

The specified drug use-results survey in Japan, other Japanese cases, and overseas cases for sildenafil (PAH) were reviewed as well as Japanese and overseas clinical practice guidelines and published literature, and it was found that none of them support the onset of adverse reactions caused by co-administration of sildenafil (PAH) and amiodarone (oral dosage form).

Consequently, since no particular safety concerns deemed to be derived from the interactions between sildenafil (PAH) and amiodarone (oral dosage form) have been identified, it is not considered necessary to maintain the contraindication for co-administration of the two drugs and precaution in the Precautions for Co-administration section of the package insert is considered appropriate.

Regarding the explanation by the MAH, PMDA considers caution is still required because co-administration between the 2 drugs is currently contraindicated and does not believe sufficient data have been collected on the safety with the co-administration (between the 2 drugs). Nonetheless PMDA considers that no clinically apparent problems have been

observed regarding the safety of the co-administration of sildenafil (PAH) and amiodarone (oral dosage form) for the following reasons:

- No Japanese or overseas cases have been identified to support a judgement that the adverse reactions involving prolonged QT interval, which were used as the basis for the initial decision to contraindicate the relevant co-administration, are related to the co-administration of sildenafil and amiodarone.
- No adverse events developing in the co-administration of sildenafil (PAH) and amiodarone that require a renewed precaution have been reported in Japan and overseas.
- The US, EU, Australian, and Canadian package inserts do not contraindicate co-administration of sildenafil and amiodarone.

4. PMDA's conclusion based on the investigation results

PMDA, while acknowledging that the risk of prolonged QT interval posed by sildenafil could not be ruled out, considers the contraindication of co-administration between sildenafil (PAH) and amiodarone (oral dosage form) may be lifted for the reasons as follows provided that a precaution be added to the Precautions for Co-administration section of the package insert and appropriate pharmacovigilance and information provision be maintained in collaboration with cardiovascular specialists experienced in the treatment of fatal arrhythmia.

- No clinically apparent problems have been observed at present regarding the safety in the co-administration of sildenafil (PAH) and amiodarone (oral dosage form).
- Cases have been reported that indicate benefits of the co-administration of sildenafil (PAH) and amiodarone (oral dosage form) outweighing the risks that may be involved, in view of treating arrhythmia accompanied by right heart failure due to PAH, medical necessity, and medical environment.

Regarding the precaution included in the EU package insert of amiodarone (oral dosage form) for co-administration with sildenafil for its being a drug metabolized by CYP3A4, PMDA believes no additional precaution is necessary because a certain level of precaution has been in place, with "CYP3A4 inhibitors" noted in the Precautions for Co-administration section in the Japanese package insert of sildenafil (PAH) and "drugs metabolized by CYP3A4" noted in the Precautions for Co-administration section of the Japanese package insert of amiodarone.

For sildenafil (ED), it should be appropriate to maintain the current contraindications for co-

administration because patients for whom sexual activities are considered inappropriate such as those with cardiovascular disorder are noted as a contraindication in the package insert and medical necessity of co-administration with amiodarone (oral dosage form) is not considered significant.

Following the discussion above, PMDA decided that the package insert of sildenafil (PAH) and amiodarone (oral dosage form) may be revised as proposed in Appendix 4-1 and Appendix 4-2, respectively:

- Language concerning amiodarone (oral dosage form) will be removed from the CONTRAINDICATIONS section and the Contraindication for Co-administration section and be added to the Precautions for Co-administration section in the package insert of sildenafil (PAH) and,
- Language concerning sildenafil will be limited to sildenafil (ED) in the and the Contraindications for Co-administration section and sildenafil (PAH) be added to the Precautions for Co-administration section in the package insert of amiodarone (oral dosage form).

With respect to co-administration of sildenafil with amiodarone (injections), although different from amiodarone (oral dosage form) in the circumstances under which it is used, it should be appropriate to add “amiodarone” to the Precautions for Co-administration section with no restrictions on administration routes in line with precautions mentioned above.

5. Expert discussion

The above opinions by PMDA were supported by expert advisors with their own opinions such as that the risk of prolonged QT interval posed by sildenafil could not be ruled out but is not clear, and that the benefits of co-administration of sildenafil (PAH) and amiodarone (oral dosage form) are considered to outweigh the associated risks.

IV. Overall Evaluation

PMDA concluded that precautions in the package insert may be revised according to Appendix 4-1 and Appendix 4-2 based on the above discussions (Appendix 4 is not included. See the Detailed information on revisions of PRECAUTIONS.)

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

Appendix 1

Products investigated

	Brand name	Non-proprietary name	Approval holder	Indications	Dosage and administration
a.	Revatio Tablets 20 mg, Revatio OD Film 20 mg, Revatio Dry Syrup for Suspension 900 mg	Sildenafil citrate	Pfizer Japan Inc.	Pulmonary arterial hypertension	<Revatio Tablets/Revatio OD Film> Adults The usual oral dose is 20 mg of sildenafil administered orally three times a day. Children at 1 year old or older For patients weighing more than 20 kg: The usual oral dose is 20 mg of sildenafil administered orally three times a day. <Revatio Dry Syrup for Suspension> Adults The usual oral dose is 20 mg of sildenafil administered orally three times a day. Children at 1 year old or older For patients weighing between 8 and 20 kg: The usual oral dose is 10 mg of sildenafil administered orally three times a day. For patients weighing more than 20 kg: The usual oral dose

	Brand name	Non-proprietary name	Approval holder	Indications	Dosage and administration
					is 20 mg of sildenafil administered orally three times a day.
b.	Ancaron tab. 100, and the others	Amiodarone hydrochloride	Sanofi K.K., and the others	Treatment of the following life-threatening recurrent arrhythmias, when these conditions have not responded to other available antiarrhythmics or when alternative agents could not be used Ventricular fibrillation, ventricular tachycardia, cardiac failure (impaired cardiac function), or atrial fibrillation associated with hypertrophic cardiomyopathy	Introduction period The usual adult dose is 400 mg of amiodarone hydrochloride administered orally in 1 to 2 divided doses for 1 to 2 weeks. Maintenance period The usual adult dose is 200 mg of amiodarone hydrochloride administered orally in 1 to 2 divided doses. Note that the dose should be adjusted when necessary, depending on the age and symptom.

Appendix 2-1

Search date: June 4, 2020

Embase

Database: Embase <1974 to 2020 June 04>

Search Strategy:

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1 exp heart arrhythmia/ or (palpitation$ or cardiopalm$ or polycardia$ or arrhythmia$ or tachycardia$ or tachysystol$ or extrasystol$ or ((ventricul$ or ventricl$ or atrial$ or auricul$) adj2 (fibrillat$ or flutter$))).mp. (552721)

2 exp heart ventricle tachycardia/ or exp heart ventricle fibrillation/ or exp heart ventricle flutter/ or exp heart ventricle extrasystole/ or ((Torsade$ adj1 de adj1 Pointes$) or (Ventric$ adj3 (tachycard$ or fibrillat$ or Flutter$)) or (Prematur$ adj2 Ventric$ adj2 Contract$)).mp. (92516)

3 1 or 2 (563113)

4 (severit$ or severe$ or serious$ or critical or fatal or iethal or deadly or killer or thanatophoric or exacerbat$ or worse or precipitat$ or aggravat$).mp. (4071714)

5 exp hospitalization/ or exp hospital patient/ or ((hospital$8 adj3 (patient? or admit$3 or admission?)) or hospitaliz$ or inpatient?).mp. (1042618)

6 4 or 5 (4816755)

7 3 and 6 (160415)

8 exp pulmonary hypertension/ or ((pulmonar$ or lung$) adj2 hypertens$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (101230)

9 7 and 8 (5076)

10 exp *heart arrhythmia/ or (palpitation$ or cardiopalm$ or polycardia$ or arrhythmia$ or tachycardia$ or tachysystol$ or extrasystol$ or ((ventricul$ or ventricl$ or atrial$ or auricul$) adj2 (fibrillat$ or flutter$))).ti. (222477)

11 9 and 10 (435)

12 exp *pulmonary hypertension/ or ((pulmonar$ or lung$) adj2 hypertens$).ti. (48562)

13 11 and 12 (128)

14 limit 13 to (abstracts and english language) (104)

15 limit 14 to medline (2)

16 14 or 15 (104)

17 limit 16 to conference abstracts (47)

18 16 not 17 (57)

MEDLINE

Database: OVID MEDLINE(R) 1946-present, OVID MEDLINE(R) In-Process & Epub Ahead of Print

Search Strategy:

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1 exp Hypertension, Pulmonary/ or ((pulmonar$ or lung$) adj2 hypertens$).mp. (53733)

2 exp Arrhythmias, Cardiac/ or (palpitation$ or cardiopalm$ or polycardia$ or arrhythmia$ or tachycardia$ or tachysystol$ or extrasystol$ or ((ventricul$ or ventricl$ or atrial$ or auricul$) adj2 (fibrillat$ or flutter$))).mp. (299496)

3 exp Tachycardia, Ventricular/ or exp Ventricular Fibrillation/ or exp Ventricular Flutter/ or exp Ventricular Premature Complexes/ or ((Torsade$ adj1 de adj1 Pointes$) or (Ventric$ adj3 (tachycard$ or fibrillat$ or Flutter$)) or (Prematur$ adj2 Ventric$ adj2 Contract$)).mp. (56208)

4 2 or 3 (2975036)

5 (severit$ or severe$ or serious$ or critical or fatal or iethal or deadly or killer or thanatophoric or exacerbat$ or worse or precipitat$ or aggravat$).mp. (2975036)

6 3 and 5 (10156)

7 1 and 6 (85)

8 exp Hospitalization/ or exp Inpatients/ or ((hospital$8 adj3 (patient? or admit$3 or admission?)) or hospitaliz$ or inpatient?).mp. (577390)

9 5 or 8 (3398544)

10 4 and 9 (59753)

11 1 and 10 (962)

12 exp *Hypertension, Pulmonary/ or ((pulmonar$ or lung$) adj2 hypertens$).ti,ab. (48931)

13 11 and 12 (902)

14 exp *Hypertension, Pulmonary/ (28051)

15 13 and 14 (212)

16 exp *Arrhythmias, Cardiac/ or exp *Tachycardia, Ventricular/ or exp *Ventricular Fibrillation/ or exp *Ventricular Flutter/ or exp *Ventricular Premature Complexes/ (160588)

17 15 and 16 (51)

Ichushi Web

#1 不整脈/TH or (不整脈/TH or 不整脈/AL) or ("不整脈"/TH or "Arrhythmias, Cardiac"/AL) or (不整脈/TH or Arrhythmia/AL) or (不整脈/TH or Arrythmia/AL) or ("不整脈"/TH or "Cardiac Dysrhythmia"/AL) or ("不整脈"/TH or "Irregular Pulse"/AL) or ("不整脈"/TH or "Pulsus Heterochronicus"/AL) or ("不整脈"/TH or "Pulsus Irregularis"/AL) or (不整脈/TH or 三段脈/AL) or (不整脈/TH or 心律動異常/AL) or ((心拍数/TH or 動悸/AL) or (頻拍/TH or 動悸/AL) or (不整脈/TH or 動悸/AL)) or (不整脈/TH or 脈拍異常/AL) or 不整脈-洞性/TH or 不整脈-心室性/TH or 不整脈-呼吸性洞性/TH or (心房細動/TH or 心房細動/AL) or (心房粗動/TH or 心房粗動/AL) [162,845 events]

#2 肺高血圧症/TH or (肺高血圧症/TH or 肺高血圧症/AL) or Ayerza/AL or "Pulmonary Arterial Hypertention"/AL or ("肺高血圧症"/TH or "Pulmonary Hypertension"/AL) or ("肺高血圧症"/TH or "Pulmonary Hypertension"/AL) or (肺高血圧症/TH or 肺血管昇圧/AL) or (肺動脈/TH or 肺動脈/AL) [53,902 events]

#3 #1 and #2 [1,989 events]

#4 重篤/AL or 重症/AL or 致死/AL [303,850 events]

#5 #3 and #4 [285 events]

#6 (#5) and (DT=2018:2020) [34 events]

#7 (#3) and (DT=2018:2020) [189 events]

#8 (#7) and (AB=Y and PT=会議録除く) [114 events]

Appendix 2-2

Search date: June 4, 2020

Embase

Database: Embase <1974 to 2020 June 04>

Search Strategy:

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1 exp amiodarone/ or amiodarone.mp. or Aldarin.mp. or aldarone.mp. or Amidaron.mp. or amidarone.mp. or amidarone chlorhydrate.mp. or amidodacore.mp. or aminodarone.mp. or amiobal.mp. or amiobeta.mp. or amiocar.mp. or amiodacore.mp. or amiodar.mp. or amiodarex.mp. or amiodaron.mp. or amiodarona.mp. or amiodarone chlorhydrate.mp. or amiodarone hydrochloride.mp. or amiogamma.mp. or amiohexal.mp. or amiorit.mp. or amiotach.mp. or amniodarone.mp. or amyodarone.mp. or ancaron.mp. or ancoron.mp. or angiodarona.mp. or angoron.mp. or aratac.mp. or arycor.mp. or atlansil.mp. or braxan.mp. or cardinorm.mp. or cardiorona.mp. or corbionax.mp. or cordarex.mp. or cordaron.mp. or cordarone.mp. or cordarone.mp. or cordarone x.mp. or cordorone.mp. or cornaron.mp. or coronovo.mp. or darmil.mp. or daronal.mp. or diarona.mp. or escodaron.mp. or eurythmic.mp. or forken.mp. or hexarone.mp. or kendaron.mp. or I 34.mp. or I 3428.mp. or miodar.mp. or miodaron.mp. or miodrone.mp. or nexterone.mp. or pacerone.mp. or procor.mp. or riva amiodarone.mp. or riva-amiodarone.mp. or rivodaron.mp. or rythmarone.mp. or sedacoron.mp. or sedacorone.mp. or tachydaron.mp. or tiaryt.mp. or trangorex.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (38825)

2 exp SILDENAFIL/ or SILDENAFIL$.mp. or REVATIO.mp. or VIAGRA.mp. or ACETILDENAFIL.mp. or HEMOSILDENAFIL.mp. or HYDROXYHOMOSILDENAFIL.mp. or NCX 911.mp. or NCX911.mp. or UK 92480 10.mp. or UK92480 10.mp. or UK 9248010.mp. or UK9248010.mp. (22250)

3 1 and 2 (326)

4 exp combination drug therapy/ or exp drug combination/ or CB.fs. or (combin$ or concurren$ or concomitant$ or plus or "add" or addon or added or additional or simultaneous$ or coadminist$ or coappl$).mp. (5337192)

5 3 and 4 (158)

6 exp *SILDENAFIL/ or (SILDENAFIL$ or REVATIO or VIAGRA or ACETILDENAFIL or HEMOSILDENAFIL or HYDROXYHOMOSILDENAFIL or NCX 911 or NCX911 or UK 92480 10).ti,ab. (11617)

7 5 and 6 (21)

8 limit 7 to (abstracts and english language) (18)

MEDLINE

Database: OVID MEDLINE(R) 1946-present, OVID MEDLINE(R) In-Process & Epub Ahead of Print

Search Strategy:

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1 exp Sildenafil Citrate/ or SILDENAFIL$.mp. or REVATIO.mp. or VIAGRA.mp. or ACETILDENAFIL.mp. or HEMOSILDENAFIL.mp. or HYDROXYHOMOSILDENAFIL.mp. or NCX 911.mp. or NCX911.mp. or UK 92480 10.mp. or UK92480 10.mp. or UK 9248010.mp. or UK9248010.mp. or 3M7OB98Y7H.mp. (7834)

2 exp Amiodarone/ or Amiodaron$.mp. or amiobeta.mp. or amiodarex.mp. or amiohexal.mp. or aratac.mp. or braxan.mp. or corbionax.mp. or cordarex.mp. or cordarone.mp. or kordaron.mp. or "l 3428".mp. or "l-3428".mp. or "l3428".mp. or ortacrone.mp. or rytmarone.mp. or "skf 33134 a".mp. or "skf 33134-a".mp. or "skf 33134a".mp. or tachydaron.mp. or trangorex.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (11035)

3 1 and 2 (18)

4 limit 3 to (abstracts and english language) (15)

Ichushi Web

#1 Amiodarone/TH or (Amiodarone/TH or Amiodarone/AL) or (Amiodarone/TH or アミオダロン/AL) or (Amiodarone/TH or 51087-N/AL) or (Amiodarone/TH or Amiobeta/AL) or (Amiodarone/TH or Amiodarex/AL) or (Amiodarone/TH or Amiodarona/AL) or ("Amiodarone"/TH or "Amiodarone Hydrochloride"/AL) or (Amiodarone/TH or Amiohexal/AL) or (Amiodarone/TH or Ancaron/AL) or (Amiodarone/TH or Aratac/AL) or (Amiodarone/TH or Braxan/AL) or (Amiodarone/TH or Corbionax/AL) or (Amiodarone/TH or Cordarex/AL) or (Amiodarone/TH or Cordarone/AL) or (Amiodarone/TH or Kordaron/AL) or ("Amiodarone"/TH or "L 3428"/AL) or (Amiodarone/TH or L-3428/AL) or (Amiodarone/TH or L3428/AL) or (Amiodarone/TH or Ortacrone/AL) or (Amiodarone/TH or Rytmarone/AL) or ("Amiodarone"/TH or "SKF 33134 A"/AL) or ("Amiodarone"/TH or "SKF 33134-A"/AL) or ("Amiodarone"/TH or "SKF 33134A"/AL) or ("Amiodarone"/TH or "SKF-33134A"/AL) or (Amiodarone/TH or TCV-3B/AL) or (Amiodarone/TH or Tachydaron/AL) or (Amiodarone/TH or Trangorex/AL) or (Amiodarone/TH or アミオダロン塩酸塩/AL) or (Amiodarone/TH or アンカロン/AL) or (Amiodarone/TH or 塩酸アミオダロン/AL) [4,862 events]

#2 Sildenafil/TH or (Sildenafil/TH or SILDENAFIL/AL) or (Sildenafil/TH or シルデナフィル/AL) or (Sildenafil/TH or Aphrodil/AL) or (Sildenafil/TH or REVATIO/AL) or (Sildenafil/TH or レバチオ/AL) or (Sildenafil/TH or バイアグラ/AL) or ("Sildenafil"/TH or "NCX 911"/AL) or (Sildenafil/TH or NCX-911/AL) or (Sildenafil/TH or NCX911/AL) or (Sildenafil/TH or UK92480/AL) or (Sildenafil/TH or UK-92480/AL) or ("Sildenafil"/TH or "UK 92480 10"/AL) or ("Sildenafil"/TH or "UK 92480"/AL) [2,808 events]

#3 #1 and #2 [12 events]

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

Appendix 3

Statements in overseas package inserts

Sildenafil（PAH）	
US package insert (USPI) (February 2018 edition)	Prolonged QT interval: No related statements included * Co-administration with amiodarone: Not related statements included *Cardiovascular events reported in association with sildenafil indicated for erectile dysfunction are described as follows: 6 ADVERSE REACTIONS 6.2 Postmarketing Experience Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

EU package insert (SPC) (April 2020 edition)	Prolonged QT interval: No related statements included* Co-administration with amiodarone: No related statements included * Cardiovascular events reported in association with sildenafil indicated for erectile dysfunction are described follows: 4. CLINICAL PARTICULARS 4.4 Special warnings and precautions for use Cardiovascular risk factors In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported in temporal association with the use of sildenafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.
Canadian package insert (June 2020 edition)	Prolonged QT interval: No related statements are included. *Non-clinical studies are mentioned. Co-administration with amiodarone: Not related statements are included. *Cardiovascular events reported in association with sildenafil indicated for erectile dysfunction are described as follows: WARNINGS AND PRECAUTIONS Cardiovascular risk factors

	In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). ADVERSE REACTIONS Post-Market Adverse Drug Reactions Cardio-vascular system In post-marketing experience with sildenafil citrate at doses indicated for male erectile dysfunction (MED), serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil citrate, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Australian package insert (October 2020 edition)	Prolonged QT interval: No related statements included * Co-administration with amiodarone: Not related statements included *Cardiovascular events reported in association with sildenafil indicated for erectile dysfunction are described follows: 4. CLINICAL PARTICULARS 4.4 Special warnings and precautions for use Cardiovascular events In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors or to other factors. Post Marketing Experience Cardiovascular In post marketing experience at doses indicated for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack and hypertension, have been reported post marketing in temporal association with the use of sildenafil.

	Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors. Tachycardia, hypotension, syncope, and epistaxis have also been reported post marketing.
Amiodarone (oral dosage form)	
US package insert (USPI)(February 2020 edition)	Co-administration with sildenafil: No related statements are included.
EU package insert (SPC) (June 2020 edition)	4. CLINICAL PARTICULARS 4.5 Interactions with other Medicinal Products and Other Forms of Interaction <u>EFFECT OF CORDARONE ON OTHER MEDICINAL PRODUCTS</u> · CYP P450 3A4 substrates When such drugs are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity. Other drugs metabolised by CYP 3A4: lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.
Canadian package insert	Co-administration with sildenafil: No related statements are included.

(December 2020 edition)	
Australian package insert (August 2020 edition)	4. CLINICAL PARTICULARS 4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS *CYP 3A4 substrates* When such drugs are coadministered with amiodarone, an inhibitor of CYP3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity: -Other drugs metabolised by CYP 3A4: Lignocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.