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Report on Investigation Results

March 16, 2020

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Brand name]	See Appendix 1
[Non-proprietary name]	See Appendix 1
[Approval holder]	See Appendix 1
[Indications]	See Appendix 1
[Dosage and administration]	See Appendix 1
[Investigation office]	Office of Pharmacovigilance I

II. Investigation background

Selexipag, clopidogrel sulfate (hereinafter referred to as “clopidogrel”), and clopidogrel/aspirin are approved for marketing with the indications and dosage and administration stated in Appendix 1.

As it was considered appropriate to contraindicate the co-administration of selexipag and preparations containing clopidogrel based on the following information obtained on selexipag and preparations containing clopidogrel after their commercial launch, each package insert contains the precaution for the co-administration of these drugs in the CONTRAINDICATIONS and Contraindications for Co-administration sections.

- An overseas clinical study (AC-065-113 Study) was conducted to investigate the effects on pharmacokinetics of selexipag and its active metabolite (MRE-269) in healthy adults when selexipag was co-administered with gemfibrozil, a strong CYP2C8 inhibitor. As a result, C_{max} and $AUC_{0-\infty}$ of selexipag increased by 1.4-fold and 2.0-fold, respectively, while C_{max} and $AUC_{0-\infty}$ of MRE-269 increased by 3.6-fold and 11-fold, respectively when selexipag was co-administered with gemfibrozil compared to those when the drug was administered alone.[1] The results exceeded the changes in exposure of selexipag and MRE-269 when CYP2C8 was inhibited estimated at the marketing-approval review

[1] Bruderer S, et al. Br J Clin Pharmacol. 2017; 83: 2778-88

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based on *in vitro* studies for selexipag. The study indicated that the contribution of CYP2C8 to metabolism of selexipag and MRE-269 would be greater than the level assumed at the review for marketing approval.

- Given the above study results, when clopidogrel, which is considered as a "strong index inhibitor" of CYP2C8 as gemfibrozil according to the US Drug Development and Drug Interactions[2] (September 2016 version), is co-administered with selexipag, the AUC of MRE-269 can increase approximately to the same level observed when selexipag is co-administered with gemfibrozil. In that case, an increase in the exposure to MRE-269 may intensify serious adverse reactions, such as hypotension.

The Pharmaceuticals and Medical Devices Agency (hereinafter, PMDA) performed this investigation in response to a request for consultation received from the marketing authorization holder (MAH) of selexipag over deleting the statement regarding clopidogrel provided in the CONTRAINDICATIONS and Contraindications for Co-administration sections and adding CYP2C8 inhibitors in the Precautions for Co-administration section of the package insert of selexipag, mainly based on the results from a drug-interaction study of selexipag and clopidogrel (AC-065-117 Study).

PMDA held an Expert Discussion as part of the investigation. The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Summary of documents submitted by the marketing authorization holder

In this section, the dose of "clopidogrel sulfate" is meant to be the equivalent dose of "clopidogrel," unless otherwise specified.

1. Discussion on drug interaction study (AC-065-117 Study)

A clinical study was conducted to investigate the effect of the co-administration with clopidogrel on the pharmacokinetics of selexipag and MRE-269. The background of the

[2] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

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study conducted is as follows: “Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil; see section 4.5)” was added in Contraindications of EU Summary of Product Characteristics (SPC) (July 2017 version) of selexipag based on the results from the AC-065-113 Study. The description includes that clopidogrel is a moderate inhibitor of CYP2C8 and that the dosing of selexipag should be adjusted when co-administration with moderate inhibitors of CYP2C8 is started or stopped. Actelion Pharmaceuticals Ltd, which developed and currently distributes selexipag overseas, planned to conduct a drug-interaction study with clopidogrel, which the company considered was used in the clinical settings particularly often among those it regarded as moderate CYP2C8 inhibitors, in order to assess the drug interaction between a moderate CYP2C8 inhibitor and selexipag. The overview of the study is as follows:

Oral selexipag at a dose of 0.2 mg twice daily for 10 days, oral clopidogrel at a dose of 300 mg at Day 4 of selexipag administration, then oral clopidogrel at a dose of 75 mg once daily from Day 5 to Day 10 were given to 22 healthy adults to investigate the effect of co-administration with clopidogrel on the pharmacokinetics of selexipag and MRE-269 and their safety (Figure 1). The observation period was determined from the initial day of selexipag to 6 - 8 days after completion of co-administration while the follow-up period was from the final day of the observation period to 30-32 days after completion of administration. The presence of adverse events was monitored until the final day of the follow-up period.

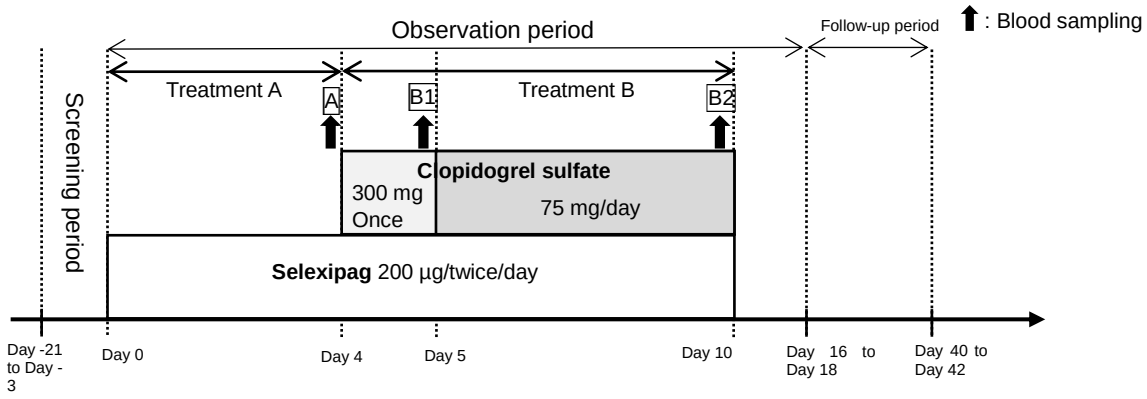

Figure 1 Summary of the study plan

The overview of PK parameters of selexipag and MRE-269 is provided in Table 1-1 and Table 1-2, respectively, while selexipag alone was administered (Figure 1A), at Day 5 of

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selexipag administration (following administration of clopidogrel 300 mg: Figure 1 B1), and at Day 10 (following repeated doses of clopidogrel 75 mg: Figure 1 B2).

Table 1-1 Effect of co-administration with clopidogrel on PK parameters of selexipag

	Selexipag administered alone (21 subjects)	Selexipag co-administered with clopidogrel 300 mg (21 subjects)	Selexipag co-administered with clopidogrel 75 mg (20 subjects)
C_{max}(ng/mL)[a]	3.08 [2.56, 3.70]	4.16 [3.48, 4.97]	3.03 [2.60, 3.53]
Ratio compared to selexipag administered alone [90% confidence interval]	-	1.35 [1.22, 1.50]	0.98 [0.89, 1.08]
AUC_{τ}(h*ng/mL)[a]	7.47 [6.35, 8.79]	10.73 [9.11, 12.65]	8.48 [7.33, 9.82]
Ratio compared to selexipag administered alone [90% confidence interval]	-	1.44 [1.32, 1.56]	1.14 [1.04, 1.26]

a: Geometric mean [95% confidence interval]

Table 1-2 Effect of co-administration with clopidogrel on PK parameters of MRE-269

	Selexipag administered alone (21 subjects)	Selexipag co-administered with clopidogrel 300 mg (21 subjects)	Selexipag co-administered with clopidogrel 75 mg (20 subjects)
C_{max}(ng/mL)[a]	3.51 [2.87, 4.28]	5.92 [5.06, 6.92]	6.62 [5.76, 7.61]
Ratio compared to selexipag administered alone [90% confidence interval]	-	1.69 [1.55, 1.84]	1.90 [1.72, 2.11]
AUC_{τ}(h*ng/mL)[a]	18.18 [15.11, 21.88]	40.87 [35.80, 46.67]	48.48 [42.69, 55.06]
Ratio compared to selexipag administered alone [90% confidence interval]	-	2.25 [2.06, 2.46]	2.70 [2.45, 2.96]

a: Geometric mean [95% confidence interval]

As for safety, the incidence of adverse reactions was 40.9% (9/22 subjects) in the period of administration of selexipag alone (Figure 1, Treatment A) and 90.5% (19/21) in the co-administration period of selexipag and clopidogrel (Figure 1, Treatment B, hereinafter, “co-administration period”). Adverse reactions that occurred in at least 2 subjects were headache in 2 subjects during the administration of selexipag alone, and headache in 7 subjects, vessel puncture site hematoma in 4 subjects, fatigue, dizziness, skin reaction, and myalgia in 2 subjects each during the co-administration period. All adverse reactions observed in this study were of mild intensity except for ‘moderate’ in 3 subjects during co-administration

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period (worsening gout, hypertriglyceridaemia, and sinusitis).

No adverse reactions that resulted in drug discontinuation were observed during the administration of selexipag alone and 1 subject experienced hematoma during the co-administration period. No serious adverse reactions including death were observed.

2. Post-marketing experience of co-administration of selexipag and clopidogrel

2-1 Drug use-results survey of selexipag

Since an all-case surveillance was required as a prerequisite for marketing approval of selexipag to collect information on the safety and effectiveness under practical use and take necessary measures for proper use, a drug use-results survey has been in place since November 2016. For this drug use-results survey, 12 cases who concomitantly received clopidogrel had been collected out of 1542 patients as of November, 2019. Of those, 8 patients developed some adverse event for which a causal relationship with the drug was reasonably possible (hereinafter, “adverse reaction”). Reported serious adverse reactions totaled 11 events in 5 patients (2 events each of diarrhoea and pleural effusion, 1 event each of hypotension, right ventricular failure, dyspnoea, deep vein thrombosis, decreased appetite, haemoptysis, and oedema). Of those, information on 1 patient was collected who was started on clopidogrel after the administration of selexipag was initiated. The adverse reactions in that patient (headache and diarrhoea, non-serious for both) had developed before the administration of clopidogrel was started. Other patients were already on clopidogrel before the administration of selexipag was started. Of these, 1 patient was started on selexipag, the patient’s diarrhoea was aggravated following an increase in the dose of selexipag, and an improvement was observed for the diarrhoea after clopidogrel was discontinued. The remaining patients who were already on clopidogrel before administration of selexipag was started included those who experienced the event after the dose of selexipag was increased, those who recovered from the event during the administration of both drugs, and those who developed the event 3 months after clopidogrel was discontinued, suggesting that the causal relationship between the co-administration of selexipag and clopidogrel and event could not be determined.

2-2. Overseas adverse reaction report and research report

After selexipag was launched, 52 overseas adverse reaction reports on patients who concomitantly received clopidogrel were submitted to PMDA (as of December, 2019).

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Common adverse reactions included death, pneumonia, pulmonary hypertension, pulmonary arterial hypertension, congestive cardiac failure, thrombosis, and disease progression. There were no patients for whom the causal relationship between the co-administration of the 2 drugs and events was strongly suggested.

There were no research reports regarding co-administration of selexipag and clopidogrel (as of December, 2019).

2-3. Other clinical studies

The MAH of selexipag conducted a placebo-controlled clinical study in Japan (Phase II Study) (hereinafter, “this study”) with 2, a dose-adjustment and a dose-maintenance period at 84 institutions between August 2016 and January 2019, in order to investigate the efficacy and safety of selexipag in patients with arteriosclerosis obliterans accompanied by intermittent claudication. Of note, co-administration of an antiplatelet agent (only 1 agent) including clopidogrel was allowed. The protocol of this study was revised to contraindicate clopidogrel for co-administration (dated March 20, 2018) after preparations that contain clopidogrel were added in the CONTRAINDICATIONS and Contraindications for Co-administration sections of the package insert of selexipag.

As for dosage and administration, the initial dose was oral selexipag 0.2 mg twice daily (0.4 mg/day). The maintenance dose was determined based on the tolerance subjects by increasing or decreasing the dose between 0.2 mg/day to the maximum of 3.2 mg/day in the dose-adjustment period (for 16 weeks). The maintenance dose was to remain unchanged throughout the 16 weeks of the dose maintenance period. If the dose needed to be changed, the drug was to be discontinued.

The incidence of adverse reactions was 44.1% (52/118 patients) in the placebo group and 81.9% (195/238) in patients on selexipag (hereinafter, “the selexipag group”). Meanwhile, the incidence in the selexipag group was 78.8% (134/170) in those without clopidogrel co-administered and 89.7% (61/68) in those with clopidogrel co-administered. Common adverse reactions (in at least 10 patients) were headache in 15 patients of the placebo group; diarrhoea, headache, pain in jaw, malaise, myalgia, and soft feces in patients who did not concurrently receive clopidogrel in the selexipag group; and pain in jaw, diarrhoea, headache and malaise in patients who concurrently received clopidogrel in the same group.

The incidence of serious adverse reactions was 1.7% (2/118 patients) in the placebo group, 0.8% (2/238) in the selexipag group, and 1.2% (2/170) in patients who did not concomitantly

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receive clopidogrel in the selexipag group. No serious adverse reactions occurred in the subjects who concurrently received clopidogrel in the selexipag group.

The percentage of patients who discontinued treatment was 16.1% (19/118 patients) in the placebo group, 16.8% (40/238) in the selexipag group, 16.5% (28/170) in the patients who did not concomitantly receive clopidogrel, and 17.6% (12/68) in those who concomitantly received clopidogrel. Common adverse reactions observed in subjects who discontinued the treatment due to development of adverse reactions (in at least 2 patients) included headache in the placebo group, malaise, diarrhoea, headache, and myalgia in subjects who did not concomitantly receive clopidogrel in the selexipag group, and headache in those who concomitantly received clopidogrel. There was no difference in the time course of discontinuation over the whole study period between the patients who concomitantly received clopidogrel and those who did not.

Table 2 provides the results with/without co-administration of clopidogrel with regard to the maintenance dose of selexipag. In the selexipag group, the maintenance dose of selexipag tended to be lower in patients who concomitantly received clopidogrel than in those who did not ($p = 0.039$).

Table 2 Maintenance dose of selexipag with/without co-administration of clopidogrel in the selexipag group

Maintenance dose of selexipag (mg/day)	Co-administration of clopidogrel				Total (213 patients)	
	Co-administered (57 patients)		Not co-administered (156 patients)			
	Number of patients	Percentage (%)	Number of patients	Percentage (%)	Number of patients	Percentage (%)
0.2	8	14.0	4	2.6	12	5.6
0.4	3	5.3	18	11.5	21	9.9
0.8	6	10.5	15	9.6	21	9.9
1.2	5	8.8	18	11.5	23	10.8
1.6	13	22.8	19	12.2	32	15.0
2.0	7	12.3	15	9.6	22	10.3
2.4	7	12.3	14	9.0	21	9.9
2.8	3	5.3	17	10.9	20	9.4
3.2	5	8.8	36	23.1	41	19.2

IV. Summary of PMDA's investigation

1. Investigation results on pharmacokinetics and safety

1-1. Investigation from a pharmacokinetic viewpoint

The MAH explains as follows about the exposure of selexipag when selexipag

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and clopidogrel are co-administered:

The results from AC-065-117 Study revealed that the exposure to MRE-269 increased when selexipag was co-administered with clopidogrel at 300 mg once daily (loading dose) or at 75 mg once daily (maintenance dose). Exposure to selexipag also increased when clopidogrel was administered at 300 mg once daily (loading dose). However, there were no marked increases, about which there had been concern based on the results from AC-065-113 Study. Therefore, PMDA considered that it would not be necessary to maintain the contraindication for co-administration with clopidogrel in the package insert. However, since a certain increase in exposure to MRE-269 was observed, it may be necessary to urge caution in the "Precautions for Co-administration" section, by means such as adding the requirement for dose adjustment considering an increased exposure to MRE-269 when clopidogrel was co-administered.

PMDA considers from a pharmacokinetic viewpoint that the risk of intensified effects due to an increase in the exposure to MRE-269 can be controlled by reducing the dose of selexipag when clopidogrel is co-administered, as described below.

- At the marketing approval review for selexipag, the subjects with moderate hepatic function disorder were allowed to receive the drug based on the precaution that "The initial dosing frequency should be reduced to once daily, and it should be considered to prolong the dosing interval and dose-increase interval and to reduce the maximum dose" in the Precautions concerning Dosage and Administration section, taking into account the submitted results below. Of note, as a result of the drug use-results survey, the incidence of adverse reactions in patients with moderate hepatic function disorder was comparable to that of patients with minor or mild hepatic function disorder.
  - The C_{max} and $AUC_{0-\infty}$ following administration of selexipag 0.4 mg increased by 2.8-fold and 4.5-fold, respectively while the C_{max} and $AUC_{0-\infty}$ of MRE-269 increased by 1.4-fold and 2.2 fold, respectively, compared to those of the subjects with normal hepatic function.
  - The plasma unbound fractions of selexipag and MRE-269 increased by approximately 1.3-fold compared to those of subjects with normal hepatic function.
- The exposure to MRE-269 when clopidogrel was co-administered is considered to be comparable to the level in the subjects with moderate hepatic function disorder, with the plasma unbound fraction taken into account, based on the results from AC-

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065-117 Study (AUC_T of MRE-269 increased by 2.25-fold following co-administration of clopidogrel 300 mg and by 2.70-fold following co-administration of 75 mg).

- Selexipag is a drug whose dose can be adjusted by titrating up or down depending on the patient's tolerance.

However, it is still expected that patients on selexipag may have the risk of intensified effects of MRE-269 when the drug is co-administered with clopidogrel and the incidence of adverse events including headache was higher after co-administered with clopidogrel although neither serious nor severe adverse events were reported. Consequently, PMDA intends to make the final conclusion based on the safety at co-administration as it requires careful consideration about the shift to "Precautions for Co-administration."

1-2. Safety when selexipag and clopidogrel are co-administered

The MAH of selexipag explained the following about the safety when selexipag and clopidogrel are co-administered:

The incidence of adverse events was higher when selexipag was co-administered with clopidogrel than when it was administered alone in AC-065-117 Study. However, the observed adverse events were neither severe nor serious. In addition, no co-administration-specific events were observed which were inconsistent with the safety profile of selexipag and clopidogrel. In addition, the ongoing drug use-results survey of selexipag has not detected any adverse reactions that may have been caused by drug interaction of selexipag and clopidogrel. Even in the clinical study in patients with arteriosclerosis obliterans accompanied by intermittent claudication, a serious adverse event occurred in 1 patient (intervertebral disc protrusion) among those who concomitantly received selexipag and clopidogrel. As the patient improved without any changes in selexipag administration, both the reporting physician and reporting company considered that causality could be ruled out. Moreover, the MAH does not consider that the situation involving the occurrence of adverse events, etc. has presented any safety problems due to co-administration. Since the common adverse events observed in the selexipag group of this study are already addressed in the related description as adverse reactions in the package insert of selexipag, the safety profile is considered similar when it is used to treat pulmonary arterial hypertension and when used to treat arteriosclerosis obliterans accompanied by intermittent claudication.

In addition, post-marketing drug reaction reports in Japan and overseas did not include any cases where interaction between the 2 drugs was suspected, either.

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Therefore, MAH considers that there have been no particular safety concerns that may be caused by interaction of selexipag and clopidogrel and that it is necessary to maintain the contraindication for co-administration with clopidogrel.

On the other hand, as the incidence of adverse reactions of selexipag can be higher when co-administered with clopidogrel than when administered alone, as shown in AC-065-117 Study, it may be necessary to urge caution to the co-administration of the drugs in the Precautions for Co-administration section.

PMDA considers what the MAH explained to be acceptable.

2. Descriptions in the relevant overseas package inserts

PMDA reviewed the statements in the overseas package inserts of selexipag and drugs that contained clopidogrel and found the following:

When both drugs became contraindicated for co-administration with each other, the US package insert (USPI) of selexipag did not state the interaction with clopidogrel while the EU SPC of selexipag noted clopidogrel as a moderate CYP2C8 inhibitor in the sections of “Special warnings and precautions for use” and “Interaction with other medicinal products and other forms of interaction in CLINICAL PARTICULARS and also that the dose of selexipag should be adjusted when clopidogrel is co-administered or discontinued. Actelion Pharmaceuticals Ltd. consulted with the US and EU regulatory agencies about a revision in the package insert of selexipag based on the results from AC-065-117 Study. Later on, the EU SPC and the USPI were revised in July, 2019 and September, 2019, respectively. The revised description is as shown in Appendix 2.

Clopidogrel was added as one of the moderate CYP2C8 inhibitors (moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide)) in the sections of DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS of the USPI (September 2019 version). It was also added that the dosing of selexipag (Uptravi) should be reduced from twice daily to once daily when clopidogrel is co-administered.

In the EU SPC (July 2019 version), a statement was added in the sections of ‘Posology and method of administration’ and “Interaction with other medicinal products and other forms of interaction” that: 1) Following administration of clopidogrel at the loading dose of 300 mg or maintenance dose of 75 mg once daily), the exposure to MRE-269 (active metabolite) increased by approximately 2.7 and 2.2-fold, and 2) the dose of selexipag should be reduced

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when clopidogrel or another moderate inhibitor of CYP2C8 is co-administered.

Meanwhile, the USPI and EU SPC of clopidogrel and clopidogrel/aspirin combination drugs have not changed the related description since PMDA considered the contraindication for co-administration. The USPI (May 2019 version) of clopidogrel states that the acyl-β-glucuronide metabolite of clopidogrel is a “strong inhibitor of CYP2C8” in the DRUG INTERACTIONS section, that co-administration of repaglinide, a CYP2C8 substrate, should be avoided, and that the dose of repaglinide should be reduced if concomitant use with clopidogrel cannot be avoided.

The EU SPC (October 2019 version) of clopidogrel and clopidogrel/aspirin combination drugs does not mention selexipag and states in the section of “Interaction with other medicinal products and other forms of interaction” that concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

3. PMDA’ decision based on the investigation results

PMDA considers that there have not been any safety concerns warranting contraindication of the co-administration of selexipag and clopidogrel, based on the extent of effects by the co-administration on the pharmacokinetics of MRE-269 and evaluation of patients who concomitantly received the 2 drugs. Therefore, co-administration of the 2 drugs should be acceptable by considering a dose reduction of selexipag when the co-administration is started. PMDA determined the following measures to be acceptable: 1) To delete the statement on clopidogrel in the CONTRAINDICATIONS and Contraindication for Co-administration sections of the package insert of selexipag and add clopidogrel in the Precautions for Co-administration section, and 2) to delete the statement on selexipag in the CONTRAINDICATIONS and Contraindication for Co-administration sections of the package insert of drugs containing clopidogrel and add selexipag in the Precautions for Co-administration section. As for the package insert of selexipag, it is considered necessary to include a precaution for other agents with moderate CYP2C8 inhibiting effects than clopidogrel as well. Consequently, PMDA determined that it is appropriate to add CYP2C8 inhibitors in the Precautions for Co-administration section.

PMDA intends to continue monitoring the safety on co-administration of selexipag and CYP2C8 inhibitors including clopidogrel in drug use-results surveys and spontaneous reports.

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4. Expert discussions

The PMDA's decision was supported by most of the experts. It is acceptable: 1) To delete the statement on clopidogrel in the CONTRAINDICATIONS and Contraindication for Co-administration sections and add CYP2C8 inhibitors in the Precautions for Co-administration section of the package insert of selexipag, and 2) To delete the statement on selexipag in the CONTRAINDICATIONS and Contraindication for Co-administration sections and add selexipag in the Precautions for Co-administration section of the package insert of preparations containing clopidogrel. However, the following comments were raised from some experts:

- Based on the results from AC-065-117 Study that administered selexipag at a dose of 0.2 mg, since the Dosage and Administration section of the package insert of selexipag specifies 0.2 to 1.6 mg per dose, the exposure may be increased further than in the study. If the tolerance data in such cases have not been obtained, evidence may be limited for supporting the transfer of co-administration with agents with CYP2C8 inhibiting effects to the Precautions for Co-administration section.
- If the co-administration with agents with CYP2C8 inhibiting effects is to be transferred to the Precautions for Co-administration section, it should be necessary to specify the criteria for dose reduction of selexipag when agents with CYP2C8 inhibiting effects are co-administered and to conduct a study to investigate the pharmacokinetics in patients on reduced and repeated dose of selexipag.
- The drug use-results survey has not detected any patients who concomitantly received selexipag and clopidogrel 300 mg (loading dose). If patients on selexipag receive a loading dose of clopidogrel, the exposure to MRE-269 may be increased more than when they receive clopidogrel 75 mg (maintenance dose). In this regard, it is desirable to select a drug with the same effect in the same class that is not affected by drug interactions, instead of clopidogrel, in the period of selexipag treatment. The package insert of selexipag should also provide this message.

PMDA considers opinions from experts as follows:

As with other prostaglandin I_2 products to treat pulmonary arterial hypertension, selexipag is to be administered to the maximum dose of each patient by titrating upward with the patient's tolerance monitored. The data discussed at the marketing approval review are limited regarding the tolerance when a dose exceeds 1.6 mg. If the dose of selexipag is titrated upward from its initial dose (0.2 mg, once) as specified in the Dosage and

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Administration of the package insert, when the administration is started during treatment with clopidogrel or other agents with CYP2C8 inhibiting effects, the dose adjustment may be acceptable within the approved doses, even if agents with CYP2C8 inhibiting effects are co-administered and thereby the exposure is increased. On the other hand, when administration of agents with CYP2C8 inhibiting effects is initiated during treatment with selexipag, a dose reduction of selexipag will be needed. No dose-reduction criteria for selexipag, however, have been specified so far. Therefore, PMDA instructed the MAH to urge caution for dose reduction of selexipag in the package insert, collect the relevant information on the safety of reduced and repeated doses of selexipag, and revise the package insert after the MAH is ready to provide additional information on its dose-reduction criteria. As the decision to select a drug in the same class as clopidogrel will depend on the patient, PMDA also instructed the MAH to properly provide the relevant information.

Moreover, initiation of clopidogrel could be required in some patients to treat their ischaemic heart disease for which percutaneous transluminal coronary angioplasty is indicated while they are receiving selexipag. In such a case, as for concerns that might be raised when the loading dose of clopidogrel is co-administered, the results from AC-065-117 Study revealed no marked difference in C_{max} and AUC_{τ} of MRE-269 between the loading dose and the maintenance dose of administered clopidogrel (see 1. Discussion on drug interaction study (AC-065-117 Study), III Summary of documents submitted by the marketing authorization holder). Therefore, PMDA considers that it is not necessarily needed to call more careful attention than the attached revision draft in the package insert at present.

V. Overall assessment

Based on the above discussion, PMDA determined that it is acceptable to delete the statement on clopidogrel in the CONTRAINDICATIONS and Contraindication for Co-administration sections of the package insert of selexipag and add CYP2C8 inhibitors in the Precautions for Co-administration section, and to delete the statement on selexipag in the CONTRAINDICATIONS and Contraindication for Co-administration sections of the package insert of preparations containing clopidogrel and add selexipag in the Precautions for Co-administration section, as mentioned in the appended revision draft (the Appendix for draft revisions is not included. See the Detailed information on revisions of PRECAUTIONS.)

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Appendix 1

Item to be investigated

Brand name	Non-proprietary name	Approval holder	Indications	Dosage and administration
Uptravi Tablets 0.2 mg, 0.4 mg	Selexipag	Nippon Shinyaku Co., Ltd.	Pulmonary arterial hypertension	The usual adult dose is started at 0.2 mg of oral selexipag after a meal twice daily. The maintenance dose should be determined with the patient's tolerance monitored by titrating up 0.2 mg at a dose with an interval of 7 days or longer to the maximum tolerance dose. Note that the maximum dose is 1.6 mg and any dose should be orally taken twice daily after a meal.
Plavix Tablets 25 mg, 75 mg, and others	Clopidogrel sulfate	Sanofi K.K., the others	○ Prevention of recurrence following ischemic cerebrovascular disorder (except cardioembolic stroke) ○ The following ischaemic heart diseases for which percutaneous transluminal coronary angioplasty (PCI) is indicated: Acute coronary syndromes (unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction)	○ Prevention from recurrence following ischemic cerebrovascular disorders (not including cardioembolic stroke) The usual adult dose is oral clopidogrel 75 mg once daily. The dose may be changed to 50 mg once daily, depending on the age, body weight, and the symptom. ○ The case of ischaemic heart disease for which percutaneous transluminal coronary angioplasty (PCI) is indicated The usual adult dose is 300 mg of oral clopidogrel once daily on Day 1 of administration, followed by

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Brand name	Non-proprietary name	Approval holder	Indications	Dosage and administration
			Stable angina pectoris, old myocardial infarction ○ Prevention from forming thrombus/embolus in patients with peripheral arterial disease	75 mg orally once daily as the maintenance dose. ○ For prevention from forming thrombus/embolus in patients with peripheral arterial disease The usual adult dose is 75 mg of oral clopidogrel once daily.
ComPlavin Combination Tablets	Clopidogrel sulfate/aspirin	Sanofi K.K.	The following ischaemic heart diseases for which percutaneous transluminal coronary angioplasty (PCI) is indicated: Acute coronary syndromes (unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction) Stable angina pectoris, old myocardial infarction	The usual oral adult dose is a tablet (equivalent to clopidogrel 75 mg and aspirin 100 mg) once daily.

Pharmaceuticals and Medical Devices Agency

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Appendix 2

	US Package Insert (USPI) (Revised September 2019)	European Package Insert (SPC) (Revised July 2019)
Selexipag	**4 CONTRAINDICATIONS** Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. **2 DOSAGE AND ADMINISTRATION** **2.4 Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors** When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI to once daily. Revert back to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. **7 DRUG INTERACTIONS** **7.1 CYP2C8 Inhibitors**	**4. CLINICAL PARTICULARS** **4.2 Posology and method of administration** *Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors* When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of Uptravi to once daily. If the therapy is not tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. Revert to twice daily dosing frequency of Uptravi when co-administration of moderate CYP2C8 inhibitor is stopped (see section 4.5). **4.3 Contraindications** Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil; see section 4.5).

Pharmaceuticals and Medical Devices Agency

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

	US Package Insert (USPI) (Revised September 2019)	European Package Insert (SPC) (Revised July 2019)
	Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated [see Contraindications (4) and Clinical Pharmacology (12.3)]. Concomitant administration of UPTRAVI with clopidogrel, a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.7-fold [see Clinical Pharmacology (12.3)]. Reduce the dosing of UPTRAVI to once daily in patients on a moderate CYP2C8 inhibitor [see Dosage and Administration (2.4)].	**4.5 Interaction with other medicinal products and other forms of interaction** Effect of other medicinal products on selexipag *Inhibitors of CYP2C8* In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold, whereas exposure to the active metabolite, the major contributor to efficacy, increased approximately 11-fold. Concomitant administration of Uptravi with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated (see section 4.3). Concomitant administration of Uptravi with clopidogrel (loading dose of 300mg or maintenance dose of 75 mg once a day), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite approximately 2.2 and 2.7-fold following loading dose and maintenance dose,

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	US Package Insert (USPI) (Revised September 2019)	European Package Insert (SPC) (Revised July 2019)
		respectively. Dosing frequency of Uptravi should be reduced to once daily when co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide). Dosing frequency of Uptravi should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped (see section 4.2).

	US Package Insert (USPI) (May 2019 Version)	European Package Insert (SPC) (October 2019 Version)
Clopidogrel sulfate	**7 DRUG INTERACTIONS** **7.6 Repaglinide (CYP2C8 Substrates)** The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Plavix can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose adjustment and appropriate monitoring. Plavix increased repaglinide exposures by 3.9-fold to 5.1-fold [see Clinical Pharmacology (12.3)]. Avoid concomitant use of repaglinide with Plavix. If concomitant use cannot be	**4. CLINICAL PARTICULARS** **4.4 Special warnings and precautions for use** CYP2C8 substrates Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5). **4.5 Interaction with other medicinal products and other forms of interaction**

Pharmaceuticals and Medical Devices Agency
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	US Package Insert (USPI) (May 2019 Version)	European Package Insert (SPC) (October 2019 Version)
	avoided, initiate repaglinide at 0.5 mg before each meal and do not exceed a total daily dose of 4 mg. Increased frequency of glucose monitoring may be required during concomitant use.	CYP2C8 substrate medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution (see section 4.4).

	US Package Insert (USPI)	European Package Insert (SPC) (October 2019 Version)
Clopidogrel sulfate/aspirin	Not marketed	**4. CLINICAL PARTICULARS** **4.4 Special warnings and precautions for use** CYP2C8 substrates Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

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	US Package Insert (USPI)	European Package Insert (SPC) (October 2019 Version)
		4.5 Interaction with other medicinal products and other forms of interaction CYP2C8 substrate medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution (see section 4.4).

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