This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of investigation results
Selexipag and preparations containing clopidogrel sulfate

March 20, 2018

Non-proprietary name

a. Selexipag

b. Clopidogrel sulfate

c. Clopidogrel sulfate/aspirin

Brand name (Marketing authorization holder)

a. Uptravi Tablets 0.2 mg, 0.4 mg (Nippon Shinyaku Co., Ltd.)

b. Plavix Tablets 25 mg, 75 mg (Sanofi K.K.) and the others

c. ComPlavin Combination Tablets (Sanofi K.K.)

Indications

a. Pulmonary arterial hypertension

b.

- Suppression of recurrent ischemic cerebrovascular disorder (not including cardioembolic stroke)
- The following ischaemic heart diseases in patients to receive treatment with percutaneous coronary artery intervention (PCI)
  Acute coronary syndrome (unstable angina pectoris, non-ST segment elevation myocardial infarction, ST segment elevation myocardial infarction),
  stable angina pectoris, old myocardial infarction
- Prevention of thrombus and embolus formation in patients with peripheral arterial disease

c. The following ischaemic heart diseases in patients to receive treatment with

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percutaneous coronary artery intervention (PCI)
Acute coronary syndrome (unstable angina pectoris, non-ST segment elevation myocardial infarction, ST segment elevation myocardial infarction),
stable angina pectoris, old myocardial infarction

Summary of revision

a.

1. “Patients receiving preparations containing clopidogrel” should be added to the Contraindications section.
2. A Contraindications for Concomitant Use section should be newly added and “Preparations containing clopidogrel” should be listed.

b., c

1. “Patients receiving selexipag” should be added to the Contraindications section.
2. A Contraindications for Concomitant Use section should be newly added and “Selexipag” should be listed.

Investigation results and background of the revision

In a drug-drug interaction study conducted overseas, markedly increased blood concentrations of selexipag and its active metabolite were observed following co-administration of selexipag and gemfibrozil (currently not approved in Japan) in comparison with the blood concentrations recorded following administration of selexipag alone, due to the inhibition of CYP2C8, the primary enzyme involved in the metabolism of selexipag. Based on these results, precautions regarding the co-administration with strong CYP2C8 inhibitors have been added to the Contraindications section of product package inserts and other labeling materials distributed in the United States. Considering the possibility of adverse drug reaction onset or symptom exacerbation arising from increased blood concentrations of selexipag and its active metabolite (which are anticipated as a result of co-administration with clopidogrel, a potent CYP2C8 inhibitor), MHLW/PMDA conducted an investigation of the evidence currently available in consultation with expert advisors, and concluded that revision of the package insert to include language regarding the risks associated with co-administration of clopidogrel was also necessary.

Number of adverse reactions and patient mortalities reported in Japan during the previous 3 fiscal years

a., b.

1 case* involving the co-administration of selexipag and clopidogrel sulfate has been reported to date. No patient mortalities have been reported to date.

a., c.

No cases involving the co-administration of selexipag and clopidogrel sulfate/aspirin have been reported to date.

*The possibility of a causal relationship with selexipag and clopidogrel sulfate was not evaluated in this case.

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