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Summary of the risk management plan (RMP) for Zontivity (vorapaxar)

This is a summary of the risk management plan (RMP) for Zontivity, which details the measures to be taken in order to ensure that Zontivity is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Zontivity, which can be found on Zontivity's EPAR page.

Overview of disease epidemiology

Zontivity is a medicine used to reduce the occurrence of atherothrombotic events (problems caused by blood clots and hardening of the arteries) such as further heart attacks or strokes in adult patients who have already had a heart attack. The risk of heart attack is greater in people of advanced age, men, people with a family history of heart disease, and in people with high blood pressure, high blood cholesterol levels, diabetes, smoking/tobacco use, alcohol use, obesity, physical inactivity, and/or stress.

Despite significant medical advances, patients who have had a heart attack continue to be at risk of a further heart attack or stroke, and have an increased risk of death. Atherothrombotic events remain the leading cause of death worldwide, with approximately 6 in 100 people who experience a heart attack dying within the first year of being discharged from the hospital.

Current therapy recommended for patients who have had a heart attack to reduce the risks described above includes aspirin, clopidogrel for those intolerant to aspirin or the combination of aspirin plus clopidogrel; in addition, patients may need medications for treatment of other common conditions (e.g. diabetes), and other lifestyle changes (e.g. reduction in cigarette smoking, weight, alcohol use).

Summary of treatment benefits

Zontivity contains the active substance vorapaxar, which helps prevent blood cells called platelets from sticking together and forming clots. It is used in combination with standard therapy (aspirin and/or other blood-thinning medicines such as clopidogrel). The benefits of Zontivity were investigated in one study involving 26,449 patients, in which the medicine was compared with placebo (a dummy treatment). A total of 13,225 patients received daily treatment with vorapaxar in addition to standard therapy, while 13,224 patients received placebo with standard therapy. The number of atherothrombotic events (heart attacks, strokes, urgent need of procedures to open blocked arteries in the heart, and death related to heart attack) was compared between the two groups.

The benefits of Zontivity were most evident in patients that entered the study with coronary artery disease (heart disease caused by the obstruction of the blood vessels that supply the heart muscle) and who did not have a prior history of stroke or transient ischemic attack ('mini stroke'); in this group, 8.5% of patients (719 out of 8,458 patients) treated with Zontivity had an atherothrombotic event, compared with 10.3% of patients (867 out of 8,439 patients) on placebo.

Unknowns relating to treatment benefits

Zontivity has not been studied in women who are pregnant or intend to become pregnant, women who are breastfeeding, children under 18 years of age, or patients with severely reduced liver function. There is no evidence to suggest that the effectiveness of Zontivity would be any different in these populations.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Medically important bleeding, including bleeding in the brain [intracranial haemorrhage (ICH)], especially among patients with a history of stroke/transient ischemic attack (TIA). A TIA (sometimes referred to as a mini stroke) is a temporary interruption of blood flow to the brain.	Because Zontivity blocks platelets from sticking together and forming blood clots, patients treated with this medicine may be at increased risk of bleeding. ICH is rare but may result in brain injury, disability or death. In clinical studies, when Zontivity was used to treat patients with a history of heart attack who did not have a prior history of stroke or TIA, severe bleeding events (defined as bleeding that resulted in death, that occurred in the brain, or that compromised blood circulation and required urgent medical attention) occurred in approximately 1 out of 100 patients, and ICH occurred in approximately 5 out of 1000 patients treated for 2.5 years on average. Patients with a history of stroke or TIA have an increased risk of ICH, and should not take Zontivity. Other factors that can increase the risk of medically important bleeding and/or ICH in general include: use of blood thinners and/or other platelet-blocking medicines, anti-inflammatory medicines (NSAIDs, for example, ibuprofen or diclofenac), high blood pressure, advanced age, low body weight (see 'important potential risks' below), smoking, alcohol consumption, and diabetes, underlying bleeding disorders or severe liver	Patients with a history of stroke, TIA, and bleeding in the brain, active bleeding such as ulcers in the stomach and intestine, and patients with bleeding tendency should not take Zontivity. Patients with severely reduced liver function are also at increased risk of bleeding. Use of Zontivity in these patients is contraindicated. Patients should talk to their doctor if they have any liver problems, and about any other medicines they are or might be taking.

Risk	What is known	Preventability
	impairment.	
Interactions with medicines that can increase blood levels of Zontivity (i.e. strong inhibitors of CYP3A4)	Certain medicines (known as 'strong inhibitors of CYP3A4', e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan) can interfere with the body's ability to eliminate Zontivity. When these medicines were taken at the same time as Zontivity, Zontivity levels in the blood were higher than when the medicine was taken alone. It is possible that higher blood levels of Zontivity could be associated with an increased risk of bleeding.	Interactions can be prevented by avoiding the use of Zontivity at the same time as other medicines known as 'strong inhibitors of CYP3A4' which could increase the blood levels of Zontivity. Patients should talk to their doctor about any other medicines they are taking or might be taking.
Interactions with medicines that can lower blood levels of Zontivity (i.e. strong inducers of CYP3A4)	Certain medicines (known as 'strong inducers of CYP3A4', e.g., rifampicin, carbamazepine and phenytoin) can increase the body's elimination of Zontivity and therefore lower the level. When these medicines were taken at the same time as Zontivity, Zontivity levels in the blood were lower than when Zontivity was taken alone. It is possible that lower blood levels of Zontivity could be associated with reduced effectiveness.	Interactions can be prevented by avoiding the use of Zontivity at the same time as medicines known as 'strong (potent) inducers of CYP3A4'. Patients should talk to their doctor about any other medicines they are taking or might be taking.

Important potential risks

Risk	What is known
Increased risk of bleeding in patients with low body weight (less than 60 kg)	In general, patients who weigh less than 60 kg are at an increased risk of bleeding if they take antiplatelet medicines. In clinical studies, the risk of bleeding with Zontivity was higher in subjects weighing less than 60 kg. However, the available data are not sufficient to draw a definite conclusion. Zontivity increases the risk of bleeding in proportion to the patient's underlying bleeding risk. Doctors should consider all factors related to the risk of bleeding before starting Zontivity.
Effects on the eye	A small number of microscopic vacuoles (fluid-filled spaces) were seen in cells in the retina (the light sensitive membrane at the back of the eye) of rats administered Zontivity. The finding was not observed in other species nor in humans. There were no measurable changes in visual function and the effect

Risk	What is known
	was reversible once treatment with Zontivity stopped. The clinical significance of this finding is currently unknown. Visual effects in humans as a result of this finding are considered very unlikely, but should patients experience any trouble with their vision, this should be discussed with their doctor.
Phospholipidosis	Phospholipidosis, the accumulation of phospholipids (a type of fats) within a cell, was observed in animals given Zontivity. The significance of this finding to people is currently unknown. No adverse effects related to phospholipidosis were noted in humans; in animals the finding was reversible, and not related to any adverse reactions.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding	Zontivity has not been studied in pregnant women, or women who are breastfeeding. Studies in pregnant animals (rabbits and rats) did not show a risk of birth defects with Zontivity treatment, but results from animal studies do not always predict what will happen in humans. Zontivity was detected in the breast milk of rats. Whether Zontivity is transferred into human breast milk is unknown. Before taking Zontivity, patients should talk to their doctor if they are pregnant or breastfeeding, or if they plan to become pregnant or to breastfeed.
Use in children and adolescents (paediatric population)	The safety and efficacy of Zontivity in children and adolescents (patients below 18 years of age) have not been established. No data are available. Therefore, Zontivity should not be given to children and adolescents.
Use in patients with severe liver impairment (problems with liver function)	Zontivity has not been studied in patients who have severe liver impairment. Patients with severe liver impairment may be at increased risk of bleeding and Zontivity is therefore contraindicated in patients with severe liver impairment. Patients should talk to their doctor if they have any liver problems.
Use together with the platelet blocking medicines prasugrel and ticagrelor, or with blood thinners taken by mouth (such as warfarin).	In the clinical studies, patients were allowed to use Zontivity in combination with other platelet blocking medicines (such as aspirin and clopidogrel). The number of patients who used the platelet blocking medicines prasugrel and ticagrelor was small, and therefore the available information about the safety of Zontivity in combination with these medicines is limited. Zontivity has not been studied in combination with blood thinners such as warfarin. Patients should talk to their doctor about any other medicines they are taking before they start taking Zontivity.
Use in patients whose platelet levels are very low	Zontivity has not been studied in patients with severe decrease in platelet levels.
Use in patients taking anti-inflammatory medicines (NSAIDs, for example,	In the clinical studies, patients were allowed to use Zontivity in combination with non-steroidal anti-inflammatory agents (NSAIDs, i.e. ibuprofen, diclofenac) other than aspirin. However the number of patients who used NSAIDs other than aspirin was small and therefore the available information

Risk	What is known
ibuprofen or diclofenac), other than aspirin	about the safety of Zontivity in combination with these medicines is limited. Patients should talk to their doctor about any other medicines they are taking before they start taking Zontivity.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Zontivity can be found on Zontivity's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Observational post authorisation safety study (PASS): Study after marketing of vorapaxar to characterise normal conditions of use and safety of vorapaxar	Collect information on the use of vorapaxar, and estimate and characterise bleeding events in the real-world clinical setting after licensing	Important identified risks: bleeding in the brain especially among patients with a history of stroke/transient ischemic attack; serious bleeding at other sites. Important identified risk: interactions with medicines that can increase blood levels of vorapaxar. Missing information: use in patients with severe liver impairment; use together with the platelet blocking medicines prasugrel and ticagrelor, or with blood thinners taken by mouth (such as warfarin)	Planned.	Interim reports will be submitted to the Agency every 2 years until study completion.

Studies which are a condition of the marketing authorisation

None.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 12-2014.