ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zontivity 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.08 mg of vorapaxar (as vorapaxar sulfate).

Excipient(s) with known effect:
Each film-coated tablet contains 66.12 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The film-coated tablets are yellow, oval-shaped, size 8.48 mm x 4.76 mm, with "351" on one side and the MSD logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zontivity is indicated for the reduction of atherothrombotic events in adult patients with

- a history of myocardial infarction (MI), co-administered with acetylsalicylic acid (ASA) and, where appropriate, clopidogrel; or
- symptomatic peripheral arterial disease (PAD), co-administered with acetylsalicylic acid (ASA) or, where appropriate, clopidogrel.

4.2 Posology and method of administration

Posology

MI
The recommended dose of Zontivity is 2.08 mg to be taken once daily. Zontivity should be initiated at least 2 weeks after a MI and preferably within the first 12 months from the acute event (see section 5.1). A delayed onset of action (at least 7 days) should be expected when starting therapy with Zontivity. There are limited data on the efficacy and safety of Zontivity beyond 24 months. Continued therapy after this time must be based on a re-evaluation of the benefits and risks for the individual of further therapy.

PAD
The recommended dose of Zontivity is 2.08 mg to be taken once daily. For patients being started on Zontivity due to symptomatic PAD, therapy may be initiated at any time.

If a dose is missed:
A patient who misses a dose of Zontivity should skip the missed dose if it is within 12 hours of the next scheduled dose and take the next dose at the regular scheduled time.

Coadministration with other antiplatelet medicinal products

MI
Patients taking Zontivity should also take acetylsalicylic acid with or without clopidogrel according to their indications or standard of care. There is limited clinical experience with prasugrel and no experience with ticagrelor in the Phase 3 studies. Therefore, vorapaxar should not be used with prasugrel or ticagrelor. Vorapaxar should not be initiated in patients taking prasugrel or ticagrelor and in case of need for additional therapy with these agents, vorapaxar should be stopped.

PAD
Patients taking Zontivity should also take acetylsalicylic acid or clopidogrel according to their indications or standard of care.

Elderly
No dose adjustment is necessary in the elderly (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2). However, reduced renal function is a risk factor for bleeding and should be considered before initiating Zontivity. There is limited therapeutic experience in patients with severe renal impairment or end stage renal disease. Therefore, Zontivity should be used with caution in such patients.

Hepatic impairment
Reduced hepatic function is a risk factor for bleeding and should be considered before initiating Zontivity. No dose adjustment is required in patients with mild hepatic impairment. Zontivity should be used with caution in patients with moderate hepatic impairment. Because of the limited therapeutic experience and the increased inherent risk of bleeding in patients with severe hepatic impairment, Zontivity is contraindicated in such patients (see sections 4.3, 4.4, and 5.2).

Paediatric population
The safety and efficacy of Zontivity in children aged less than 18 years have not yet been established. No data are available.

Method of administration
Oral use. The tablet may be taken with or without food.

4.3 Contraindications

- Patients with a history of stroke or transient ischaemic attack (TIA) (see section 5.1).
- Patients with a history of intracranial haemorrhage (ICH).
- Patients with any active pathological bleeding (see sections 4.4 and 4.8).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

General risk of bleeding
Zontivity increases the risk of bleeding, including ICH and sometimes fatal bleeding. When administered in addition to standard care, generally acetylsalicylic acid and a thienopyridine, compared with standard care alone, Zontivity increased the risk of GUSTO (Global utilization of streptokinase and tpa for occluded arteries) moderate or severe bleeding (see section 4.8).

Zontivity increases the risk of bleeding in proportion to the patient's underlying bleeding risk. The underlying risk of bleeding (e.g., recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, or active peptic ulcer disease) should be considered before initiating Zontivity. General risk factors for bleeding include older age (however, no dose adjustment is necessary in the elderly (see section 5.2)), low body weight, and reduced renal or hepatic function. In these subgroups, Zontivity should only be prescribed after careful assessment of individual potential risks and benefits and the need for co-medication that may further increase the risk of bleeding. A history of bleeding disorders and use of certain concomitant medicinal products (e.g., anticoagulant and fibrinolytic therapy, and chronic nonsteroidal anti-inflammatory drugs (NSAIDS), selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors) may also increase the risk of bleeding in patients taking Zontivity.

There is limited experience with the concomitant use of vorapaxar with warfarin or other oral anticoagulants. The combination of vorapaxar with warfarin or other oral anticoagulants may increase the risk of bleeding and should be avoided.

In patients treated with vorapaxar the concomitant use of heparin (including low molecular weight heparin (LMWH)) might be associated with an increased risk of bleeding and caution is advised.

Bleeding should be suspected in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or other surgical procedures, even if the patient does not have any signs of bleeding.

Patients with low body weight (<60 kg)
In general, a body weight <60 kg is a risk factor for bleeding. In TRA 2°P - TIMI 50, in vorapaxar-treated patients, including those with history of stroke, a higher rate of ICH was observed in patients weighing <60 kg compared to patients weighing ≥60 kg. Zontivity should be used with caution in patients with a body weight <60 kg.

Surgery
Patients should be advised to inform physicians and dentists that they are taking Zontivity before any surgery is scheduled and before any new medicinal product is taken.

In the TRA 2°P-TIMI 50 trial, although CABG-related TIMI major bleeding was observed in patients taking vorapaxar (see section 4.8), patients who continued therapy with vorapaxar while undergoing CABG did not show an increased risk of major bleeding compared to placebo. There is less information about other types of surgery but the overall evidence does not suggest an excessive risk of major bleeding. Patients undergoing urgent CABG, PCI, non CABG surgery, or other invasive procedures while on Zontivity may remain on Zontivity. However, if a patient is to undergo elective surgery, if clinically feasible, Zontivity should be discontinued at least 30 days prior to surgery.

Withholding Zontivity for a brief period will not be useful in preventing or managing an acute bleeding event because of its long half-life (see section 5.2). There is no known treatment to reverse the antiplatelet effect of Zontivity. Based on results of pre-clinical studies that investigated bleeding while on vorapaxar on the background of acetylsalicylic acid and clopidogrel, it may be possible to restore hemostasis by administering exogenous platelets. (See section 5.3.)

Severe hepatic impairment
Severe hepatic impairment increases the risk of bleeding; therefore, the use of Zontivity in these patients is contraindicated (see sections 4.2 and 5.2).

Severe renal impairment
Reduced renal function is a risk factor for bleeding and should be considered before initiating Zontivity. There is limited therapeutic experience in patients with severe renal impairment or end stage renal disease. Therefore, Zontivity should be used with caution in such patients.

Discontinuation of Zontivity
Interruption of Zontivity treatment should be avoided. If Zontivity must be temporarily discontinued, restart it as soon as possible. Patients who experience a stroke, TIA, or ICH while on Zontivity should have therapy discontinued permanently (see sections 4.8 and 5.1). Patients experiencing acute coronary syndrome (ACS) while on Zontivity can remain on Zontivity.

Lactose
Zontivity contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on vorapaxar
Vorapaxar is eliminated primarily by metabolism, with significant contribution by CYP3A. Vorapaxar is also a substrate of CYP2J2; therefore, there is a potential for potent inhibitors of CYP2J2 to result in increases in vorapaxar exposure.

Strong CYP3A inhibitors
Co-administration of ketoconazole (400 mg once-daily) with vorapaxar significantly increased the vorapaxar mean C_{max} and AUC by 93% and 96%, respectively. Concomitant use of Zontivity with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan) should be avoided.

Phase 3 data suggest that co-administration of a weak or moderate CYP3A inhibitor with vorapaxar does not increase bleeding risk or alter the efficacy of vorapaxar. No dose adjustment for vorapaxar is required in patients taking weak to moderate inhibitors of CYP3A.

Strong CYP3A inducers
Co-administration of rifampin (600 mg once-daily) with vorapaxar substantially decreased the vorapaxar mean C_{max} and AUC by 39% and 55%, respectively. Concomitant use of Zontivity with strong (potent) inducers of CYP3A (e.g., rifampin, carbamazepine and phenytoin) should be avoided.

Medicinal products that increase gastric pH
No clinically relevant differences in vorapaxar pharmacokinetics were observed following daily co-administration of an aluminium hydroxide/magnesium carbonate antacid or pantoprazole (a proton pump inhibitor).

Effects of vorapaxar on other medicinal products
Digoxin
Vorapaxar is a weak inhibitor of the intestinal P-glycoprotein (P-gp) transporter. Co-administration of vorapaxar (40 mg) and digoxin (0.5 mg single-dose) increased digoxin C_{max} and AUC by 54% and 5%, respectively. No dosage adjustment of digoxin or Zontivity is recommended. Patients receiving digoxin should be monitored as clinically indicated.

CYP2C8 substrates
Co-administration with vorapaxar did not alter the single-dose pharmacokinetics of rosiglitazone (8 mg), a CYP2C8 substrate not marketed in the EU.

Anticoagulants
When Zontivity was co-administered with warfarin, there were no alterations in the pharmacokinetics or pharmacodynamics of warfarin. Clinical experience involving co-administration of oral anticoagulants with vorapaxar is limited, and there is no experience with oral Factor Xa or Factor IIa inhibitors in the vorapaxar Phase 3 program. The coadministration of Zontivity with anticoagulants e.g., warfarin and new oral anticoagulants (NOACs), should be avoided. (See section 4.4.)

In patients treated with Zontivity the concomitant use of heparin (including LMWH) might be associated with an increased risk of bleeding and caution is advised. (See section 4.4.)

When Zontivity was co-administered with prasugrel, no clinically significant pharmacokinetic interaction was demonstrated. There is limited experience with prasugrel and no experience with ticagrelor in the vorapaxar Phase 3 studies. Vorapaxar should not be used with prasugrel or ticagrelor (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no reliable data on the use of vorapaxar in pregnant women. No relevant effects were observed in animals (see section 5.3). Zontivity should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breast-feeding
It is not known whether vorapaxar is excreted in human breast milk. Studies in rats have shown vorapaxar and/or its metabolites are excreted in milk. Due to the unknown potential for adverse reactions in breast-feeding infants from Zontivity, discontinue breast-feeding or discontinue Zontivity; taking into account the importance of the medicinal product to the mother.

Fertility
There are no data on fertility in humans administered Zontivity. No effects on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Zontivity has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reaction reported during treatment is bleeding. Among the common bleeding events, epistaxis is the most frequent.

Adverse reactions were evaluated in 19,632 patients treated with Zontivity [13,186 patients, including 2,187 patients treated for more than 3 years, in the TRA 2°P TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) study and 6,446 patients in the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) study]. The adverse reactions of bleeding in Table 1 are summarized for the TRA 2°P TIMI 50 study. Non-bleeding adverse reactions in Table 1 are summarized for both the TRA 2°P TIMI 50 and TRACER studies. (See Table 1.)

Tabulated list of Adverse Reactions

Adverse reactions are classified according to frequency and System Organ Class. Frequencies are defined as:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1: Tabulated List of Adverse Reactions

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders		Anaemia
Eye disorders		Conjunctival haemorrhage, diplopia
Vascular disorders	Haematoma	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Epistaxis	
Gastrointestinal disorders		Gastritis, Gastrointestinal haemorrhage, Gingival bleeding, Melaena, Rectal haemorrhage
Skin and subcutaneous tissue disorders	Increased tendency to bruise	Ecchymosis, Skin haemorrhage
Renal and urinary disorders	Haematuria	
Injury, poisoning, and procedural complications	Contusion	Wound haemorrhage

Description of selected adverse reactions

The adverse reactions in the vorapaxar-treated (n=10,059) and placebo-treated (n=10,049) post-MI or PAD patients with no history of stroke or TIA are shown below.

Bleeding

Bleeding category definitions:

GUSTO severe: fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention;
GUSTO moderate: bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise.

TIMI Major: Clinically apparent with >50 g/L decrease in haemoglobin or intracranial haemorrhage.

TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.

The results for the bleeding endpoints in the post-MI or PAD patients with no history of stroke or TIA are shown in Table 2.

Table 2: Non-CABG-Related Bleeds in Post-MI or PAD Patients with No History of Stroke or TIA

	Placebo (n= 10,049)		Zontivity (n=10,059)			
Endpoints	Patients with events (%)	K-M %*	Patients with events (%)	K-M %*	Hazard Ratio†,‡ (95% CI)	p-value‡
GUSTO Bleeding Categories						
Severe	105(1.0%)	1.3%	115 (1.1%)	1.3%	1.09 (0.84-1.43)	0.503
Moderate	138 (1.4%)	1.6%	229 (2.3%)	2.6%	1.67 (1.35-2.07)	<0.001
TIMI Bleeding Categories						
Major	183 (1.8%)	2.1%	219 (2.2%)	2.5%	1.20 (0.99-1.46)	0.069
Minor	80 (0.8%)	0.9%	150 (1.5%)	1.7%	1.88 (1.44-2.47)	<0.001
ICH	39 (0.4%)	0.5%	49 (0.5%)	0.6%	1.25 (0.82-1.91)	0.294
Fatal Bleeding	20 (0.2%)	0.3%	19 (0.2%)	0.3%	0.95 (0.51-1.78)	0.872

* K-M estimate at 1,080 days
† Hazard ratio is Zontivity group versus placebo group
‡ Hazard ratio and p-value were calculated based on Cox PH model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use)

The effect of Zontivity on GUSTO severe or moderate bleeding relative to placebo was shown to be consistent across the subgroups examined.

In TRA 2°P - TIMI 50, 367 post-MI or PAD patients with no history of stroke or TIA underwent CABG surgery. The percentages of patients who underwent CABG surgery and had CABG-related bleeds are shown in Table 3. Rates were similar for Zontivity and placebo.

Table 3: CABG-Related Bleeds

Post-MI or PAD Patients with No History of Stroke or TIA		
	Placebo (n=196)	Zontivity (n=171)
Endpoints	Patients with events (%)	Patients with events (%)
TIMI Bleeding Category		
Major	10 (5.1%)	11 (6.4%)
Overall Population		
	Placebo (n=230)	Zontivity (n=189)
TIMI Bleeding Category		
Major	13 (5.7%)	12 (6.3%)

Bleeding events were treated in the same manner as for other antiplatelet agents including addressing the source of bleeding while providing supportive care.

Medicinal product discontinuation
For post-MI or PAD patients with no history of stroke or TIA, the rate of study drug discontinuation because of adverse reactions was 6.8% for Zontivity and 6.9% for placebo. Bleeding was the most common adverse reaction leading to study drug discontinuation for both treatments (3.0% for Zontivity and 1.8% for placebo).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Platelet inhibition with vorapaxar is gradual and reversible. Treatment of presumed overdose should address signs and symptoms.

As vorapaxar is highly protein-bound, haemodialysis is unlikely to be effective in the treatment of an overdose.

In humans, vorapaxar has been administered in single doses up to 120 mg and daily doses of 5 mg for up to 4 weeks without observation of dose-associated adverse events or identification of a specific risk.

Platelet transfusion may be considered as supportive therapy should bleeding occur (see section 5.3).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin, ATC code: B01AC26.

Mechanism of action
Vorapaxar is a selective and reversible inhibitor of the PAR-1 receptors on platelets that are activated by thrombin.

Pharmacodynamic effects
Vorapaxar inhibits thrombin-induced platelet aggregation in in vitro studies. In addition, vorapaxar inhibits thrombin receptor agonist peptide (TRAP)-induced platelet aggregation without affecting coagulation parameters. Vorapaxar does not inhibit platelet aggregation induced by other agonists such as adenosine diphosphate (ADP), collagen or a thromboxane mimetic.

At a dose of 2.5 mg of vorapaxar sulfate (equivalent to 2.08 mg vorapaxar) daily, vorapaxar consistently achieves ≥80% inhibition of TRAP-induced platelet aggregation within one week of initiation of treatment. The duration of platelet inhibition is dose and concentration dependent. Inhibition of TRAP-induced platelet aggregation at a level of ≥80% may last for 2 to 4 weeks after discontinuation of daily doses of vorapaxar sulfate 2.5 mg. The duration of these pharmacodynamic effects is consistent with the drug's elimination half-life.

Consistent with its selective molecular target (PAR-1), vorapaxar has no effect on ADP-induced platelet aggregation in healthy subjects and patient populations.

In healthy volunteer studies, no changes in platelet P-selectin and soluble CD40 ligand (sCD40L) expression or coagulation test parameters (TT, PT, aPTT, ACT, ECT) occurred after single or multiple

dose (28 days) administration of vorapaxar. No meaningful changes in P-selectin, sCD40L and hs-CRP concentrations were observed in patients treated with vorapaxar in the Phase 2/3 clinical trials.

Evaluation of Zontivity on QTc interval
The effect of vorapaxar on the QTc interval was evaluated in a thorough QT study and in other studies. Vorapaxar had no effect on the QTc interval at single doses up to 120 mg.

Clinical efficacy and safety
Zontivity has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

The clinical evidence for the effect of Zontivity in patients with a history of myocardial infarction, defined as a spontaneous MI ≥2 weeks but ≤12 months prior, is derived from TRA 2°P - TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events). TRA 2°P - TIMI 50 was a multicenter, randomized, double-blind, placebo-controlled study conducted in patients who had evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems. Patients were randomized to receive daily treatment with 2.5 mg vorapaxar sulfate (n=13,225) or placebo (n=13,224) in addition to other standard therapy. The study's primary endpoint was the composite of cardiovascular death, MI, stroke, and UCR. The composite of cardiovascular death, MI, and stroke were assessed as secondary endpoint. The median duration of treatment with vorapaxar was 823 days (interquartile range: 645-1016 days).

The findings for the primary efficacy composite endpoint show a 3-year Kaplan-Meier (K-M) event rate of 11.2% in the Zontivity group compared with that of 12.4% in the placebo group (Hazard Ratio [HR]: 0.88; 95% Confidence Interval [CI], 0.82 to 0.95; p=0.001) and demonstrated superiority of Zontivity over placebo in preventing CV death, MI, stroke, or UCR.

The findings for the key secondary efficacy endpoint, a 3-year K-M event rate of 9.3% in the Zontivity group compared with that of 10.5% in placebo group (HR: 0.87; 95% CI, 0.80 to 0.94; p <0.001).

Although the TRA 2°P - TIMI 50 trial was not designed to evaluate the relative benefit of Zontivity in individual patient subgroups, the benefit was most apparent in patients who were enrolled on the basis of a recent MI as indicated by a history of spontaneous MI ≥2 weeks but ≤12 months prior (post-MI or PAD patient population) with no history of stroke or TIA. Of these patients, 10,080 received Zontivity (8,458 post-MI and 1,622 PAD) and 10,090 received placebo (8,439 post-MI and 1,651 PAD) in addition to standard of care, including antiplatelet therapy with acetylsalicylic acid and thienopyridine. Of the patients with MI without a history of stroke or TIA, 21% were receiving acetylsalicylic acid without thienopyridine, 1% was receiving a thienopyridine without acetylsalicylic acid, and 77% were receiving both acetylsalicylic acid and a thienopyridine when they enrolled in the trial. Of the patients with PAD without a history of stroke or TIA, 61% were receiving acetylsalicylic acid without thienopyridine, 8% were receiving a thienopyridine without acetylsalicylic acid, and 27% were receiving both acetylsalicylic acid and a thienopyridine when they enrolled. In post-MI and PAD patients, the median duration of treatment with Zontivity in these patients was 2.5 years (up to 4 years). This background therapy was to be continued during the trial at the treating physician's discretion, per standard of care.

The post-MI patient population with no history of stroke or TIA was 88% Caucasian, 20% female, and 29% ≥65 years of age, with a median age of 58 years, and included patients with diabetes (21%) and patients with hypertension (62%). The median Body Mass Index was 28.

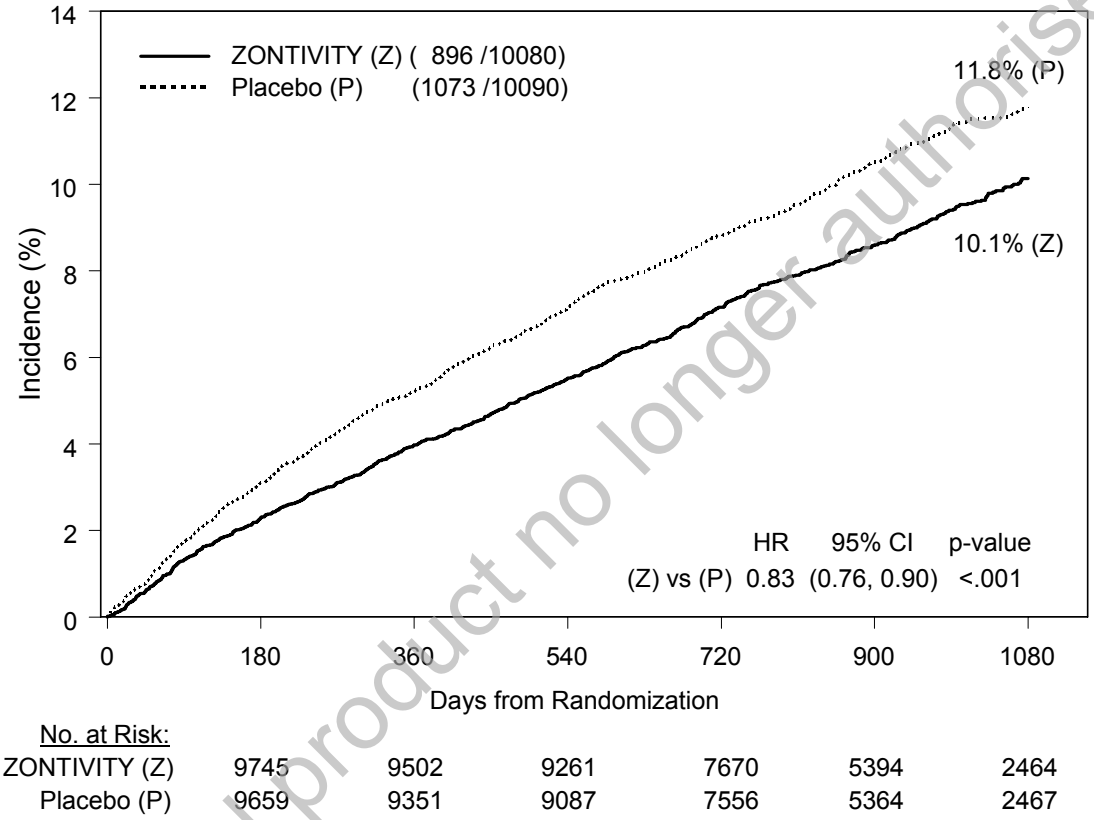
The PAD patient population with no history of stroke or TIA was 90% Caucasian, 29% female, and 57% ≥65 years of age, with a median age of 66 years, and included patients with diabetes (35%) and patients with hypertension (82%). The median Body Mass Index was 27.

In the cohort of post-MI or PAD patients with no history of stroke or TIA, the findings for the primary and key secondary composite endpoints are consistent with the overall population (see Figure 1 and Table 4).

Among patients with a qualifying MI, Zontivity was initiated at least 2 weeks after the MI and within the first 12 months from the acute event. Within that period the effect was similar regardless of the time from qualifying MI to the start of therapy with Zontivity.

The treatment effect of vorapaxar on the primary and key secondary endpoints was shown to be durable and persistent over the length of the TRA 2°P - TIMI 50 study.

Figure 1: Time to First Occurrence of CV death, MI, Stroke or UCR in Post-MI or PAD Patients with No History of Stroke or TIA



No. at Risk:

ZONTIVITY (Z)	9745	9502	9261	7670	5394	2464
Placebo (P)	9659	9351	9087	7556	5364	2467

Table 4: Primary and Key Secondary Efficacy Endpoints in Post-MI or PAD Patients with No History of Stroke or TIA

	Placebo (n=10,090)		Zontivity (n=10,080)			
Endpoints	Patients with events* (%)	K-M %†	Patients with events* (%)	K-M %†	Hazard Ratio‡,§ (95% CI)	p-value§
Primary Efficacy Endpoint (CV death/MI/stroke/UCR)	1,073 (10.6%)	11.8%	896 (8.9%)	10.1%	0.83 (0.76-0.90)	<0.001
CV Death	154 (1.5%)		129 (1.3%)			
MI	531 (5.3%)		450 (4.5%)			
Stroke	123 (1.2%)		91 (0.9%)			
UCR	265 (2.6%)		226 (2.2%)			
Key Secondary Efficacy Endpoint (CV death / MI / stroke) §	851 (8.4%)	9.5%	688 (6.8%)	7.9%	0.80 (0.73-0.89)	<0.001
CV Death	160 (1.6%)		132 (1.3%)			
MI	562 (5.6%)		464 (4.6%)			
Stroke	129 (1.3%)		92 (0.9%)			

* Each patient was counted only once (first component event) in the component summary that contributed to the primary efficacy endpoint

† K-M estimate at 1,080 days

‡ Hazard ratio is Zontivity group versus placebo group

§ Cox proportional hazard model with covariates treatment and stratification factors (qualifying atherosclerotic disease and planned thienopyridine use)

In the cohort of post-MI or PAD patients with no history of stroke or TIA, the net clinical outcome analysis based on multiple occurrences of endpoints (CV Death/MI/Stroke/GUSTO Severe) is constant over time at each of the censoring times examined (12, 18, 24, 30, and 36 months) at cumulative 6-month intervals. (See Table 5.)

Table 5: Multiple Occurrences of Net Clinical Outcome (CV Death/MI/Stroke/GUSTO Severe*) in Post-MI or PAD Patients with No History of Stroke or TIA

	Placebo n=10,049	Zontivity n=10,059	Hazard Ratio†,‡ (95% CI)	p-value‡
Randomization to 12 months				
Total Events	474	401	0.83 (0.73 - 0.95)	0.008
Patients with only one Event	337	269		

	Placebo n=10,049	Zontivity n=10,059	Hazard Ratio[†,‡] (95% CI)	p-value[‡]
Patients with two Events	49	47		
Patients with ≥3 Events	11	12		
Randomization to 18 months				
Total Events	703	564	0.79 (0.71 - 0.89)	<0.001
Patients with only one Event	463	361		
Patients with two Events	82	67		
Patients with ≥3 Events	21	21		
Randomization to 24 months				
Total Events	903	741	0.81 (0.73 - 0.89)	<0.001
Patients with only one Event	554	456		
Patients with two Events	114	80		
Patients with ≥3 Events	34	38		
Randomization to 30 months				
Total Events	1,070	893	0.82 (0.75 - 0.90)	<0.001
Patients with only one Event	658	524		
Patients with two Events	121	102		
Patients with ≥3 Events	46	48		
Randomization to 36 months				
Total Events	1,166	987	0.83 (0.76 - 0.91)	<0.001
Patients with only one Event	700	569		
Patients with two Events	138	112		
Patients with ≥3 Events	52	55		

[*] Includes all CV Death, MI, Stroke and GUSTO severe events up to each timepoint as indicated in the table.
[†] Hazard Ratio is vorapaxar group versus placebo group.
[‡] Hazard Ratio and p-value were calculated based on Andersen-Gill model with covariates treatment and stratification factor (planned thienopyridine use).

In post-MI or PAD patients with no history of stroke or TIA, an analysis of multiple occurrences of adjudicated endpoints indicates that Zontivity was associated with a reduction in the incidence of recurrent events.

Among post-MI or PAD patients without a history of stroke or TIA, Zontivity appeared to reduce the rate of definite stent thrombosis (HR 0.71 (0.51-0.99 for adjudicated “definite”) vs. placebo in subjects receiving any stent before or during the study.

Patients with a history of PAD but without a history of stroke or TIA randomized to vorapaxar had fewer peripheral revascularization procedures (15.4% v 19.3%, 3-year KM rates; HR 0.82 [0.71-0.94, 95% CI]; P=0.005) and fewer hospitalizations for acute limb ischemia (2.0% v 3.3%; HR 0.59 [0.40 – 0.86]; P=0.007) than patients randomized to placebo.

The treatment effect of Zontivity was consistent with the overall results across many subgroups, including sex; age; renal insufficiency; medical history of diabetes mellitus; tobacco use; concomitant therapies at baseline including thienopyridine, acetylsalicylic acid, and statins.

In TRA 2°P - TIMI 50, among patients who entered the trial, those with a history of ischaemic stroke had a higher 3 year K-M event rate for ICH on Zontivity plus standard care (2.7%) than on standard care alone (0.9%). In post-MI or PAD patients with no history of stroke or TIA, the 3 year K-M event rates for ICH were 0.6% and 0.5% for Zontivity plus standard care and standard care alone, respectively.

In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial, comprising patients with a NSTEACS (non-ST segment elevation acute coronary syndrome) who were largely antiplatelet naive, vorapaxar, with a loading dose of 40 mg and then maintained at 2.5 mg/day in addition to standard of care, initiated within 24 hours of NSTEACS, did not achieve its primary efficacy endpoint (cardiovascular death, MI, stroke, urgent coronary revascularization, and recurrent ischemia with rehospitalisation) and there was an increased risk of GUSTO moderate or severe bleeding.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Zontivity in one or more subsets of the paediatric population in prevention of arterial thromboembolism (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
After oral administration of a single vorapaxar sulfate 2.5 mg dose, vorapaxar is rapidly absorbed and peak concentrations occur at a median t_{max} of 1 hour (range: 1 to 2) under fasted conditions. The mean absolute bioavailability of vorapaxar from the 2.5 mg dose of vorapaxar sulfate is 100%.

Ingestion of vorapaxar with a high-fat meal resulted in no meaningful change in AUC with a small (21%) decrease in C_{max} and delayed t_{max} (45 minutes). Zontivity may be taken with or without food. Co-administration of an aluminium hydroxide/magnesium carbonate antacid or proton pump inhibitor (pantoprazole) did not affect vorapaxar AUC with only small decreases in C_{max}. Therefore, Zontivity may be administered without regard to co-administration of agents that increase gastric pH (antacid or proton pump inhibitor).

Distribution
The mean volume of distribution of vorapaxar is approximately 424 litres. Vorapaxar and the major circulating active metabolite, M20, are extensively bound (≥99%) to human plasma proteins. Vorapaxar is highly bound to human serum albumin and does not preferentially distribute into red blood cells.

Biotransformation
Vorapaxar is eliminated by metabolism, with CYP3A4 and CYP2J2 responsible for formation of M20, its major active circulating metabolite, and M19, the predominant metabolite identified in excreta. The systemic exposure of M20 is ~20% of the exposure to vorapaxar.

Elimination
The primary route of elimination is through the faeces, with approximately 91.5% of radiolabeled dose predicted to be recovered in the faeces compared to 8.5% in the urine. Vorapaxar is eliminated primarily in the form of metabolites, with no vorapaxar detected in urine. The apparent terminal half-life for vorapaxar is 187 hours (range 115-317 hours) and is similar for the active metabolite.

Linearity/non-linearity
Vorapaxar exposure increases in an approximately dose-proportional manner following single doses of 1 to 40 mg and multiple doses of 0.5 to 2.5 mg of vorapaxar sulfate. The systemic pharmacokinetics of

vorapaxar are linear with accumulation (6-fold) predictable from single- to multiple-dose data. Steady-state is achieved by 21 days following once-daily dosing.

Specific populations
The effects of renal (end-stage renal disease undergoing haemodialysis) and hepatic impairment on the pharmacokinetics of vorapaxar were evaluated in specific pharmacokinetic studies and are summarized below:

Renal Impairment
Pharmacokinetics of vorapaxar are similar between patients with end-stage renal disease (ESRD) undergoing haemodialysis and healthy subjects. Based on population pharmacokinetic analysis using data from healthy subjects and patients with atherosclerotic disease, vorapaxar mean AUC is estimated to be higher in patients with mild (17%) and moderate (34%) renal impairment compared to those with normal renal function; these differences are not considered to be clinically relevant. No dose adjustment is necessary for patients with renal impairment, including subjects with ESRD. There is limited therapeutic experience in patients with severe renal impairment or end stage renal disease. Therefore, Zontivity should be used with caution in such patients.

Hepatic Impairment
Pharmacokinetics of vorapaxar are similar between patients with mild (Child Pugh, 5 to 6 points) to moderate (Child Pugh, 7 to 9 points) hepatic impairment and healthy patients. Reduced hepatic function is a risk factor for bleeding and should be considered before initiating Zontivity. No dose adjustment is required for patients with mild hepatic impairment. Zontivity should be used with caution in patients with moderate hepatic impairment. Zontivity is contraindicated in patients with severe hepatic impairment (Child Pugh, 10 to 15 points) (see sections 4.3 and 4.4).

Age, gender, weight and race were included as factors assessed in the population pharmacokinetic model to evaluate vorapaxar pharmacokinetics in healthy subjects and patients:

Elderly
Pharmacokinetics of vorapaxar are similar between elderly, including those ≥75 years of age, and younger patients. No dose adjustment is necessary (see section 4.4).

Gender
The mean estimated vorapaxar C_{max} and AUC were 30% and 32% higher, respectively, in females compared to males. These differences are not considered to be clinically relevant and no dose adjustment is necessary.

Weight
The mean estimated vorapaxar C_{max} and AUC were 35% and 33% higher, respectively, in patients with a body weight of <60 kg compared to those weighing 60-100 kg. By comparison, vorapaxar exposure (AUC and C_{max}) is estimated to be 19-21% lower in patients with a body weight of >100 kg compared to those weighing 60-100 kg. In general, a body weight <60 kg is a risk factor for bleeding. Zontivity should be used with caution in patients with a body weight <60 kg.

Race
The mean estimated vorapaxar C_{max} and AUC were 24% and 22% higher in Asian patients compared to that of Caucasians. Vorapaxar exposure (AUC and C_{max}) in patients of African descent is estimated to be 17-19% lower compared to that of Caucasians. These differences are not considered to be clinically relevant and no dose adjustment is necessary.

Drug Interactions
Effects of vorapaxar on other medicinal products
In vitro metabolism studies demonstrate that vorapaxar is unlikely to cause clinically significant inhibition of human CYP1A2, CYP2B6, CYP3A, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. No clinically meaningful inhibition of CYP2B6, CYP3A, CYP2C19, or CYP2D6 by M20 is expected. In addition, no clinically meaningful inhibition of OATP1B1, OATP1B3, BCRP, OAT1, OAT3, and

OCT2 by vorapaxar or M20 is anticipated. Based upon *in vitro* data, chronic administration of vorapaxar is unlikely to induce the metabolism of drugs metabolized by major CYP isoforms.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and fertility.

In repeat dose oral toxicity studies in rodents and monkeys, the principal treatment-related findings were urinary bladder and ureter hyperplasia in mice, hepatic vascular thrombi, lymphoid necrosis and retinal vacuolation in rats and phospholipidosis in all species. Phospholipidosis occurs at acceptable human to animal safety margins and was reversible. The clinical significance of this finding is currently unknown.

No defects were observed in embryo-foetal developmental studies in rats and rabbits at exposures sufficiently in excess of human exposure at the recommended human dose (RHD). Pre and postnatal studies in rats only showed some inconsistent developmental effects at exposures sufficiently in excess of human exposure at the RHD of 2.08 mg vorapaxar. The overall no effect level for the pre- and postnatal development effects was 5 mg/kg/day (6.8-times [female animals] the human steady-state exposure at 2.5 mg/day).

Vorapaxar had no effects on fertility of male and female rats at exposures sufficiently in excess of human exposure at the RHD.

Vorapaxar was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Vorapaxar did not increase bleeding time in non-human primates when administered alone at 1 mg/kg. Bleeding time was prolonged slightly with administration of acetylsalicylic acid alone or in combination with vorapaxar. Acetylsalicylic acid, vorapaxar, and clopidogrel in combination produced significant prolongation of bleeding time. Transfusion of human platelet rich plasma normalised bleeding times with partial recovery of ex vivo platelet aggregation induced with arachidonic acid, but not induced with ADP or TRAP. Platelet poor plasma had no effect on bleeding times or platelet aggregation. (See section 4.4.)

No vorapaxar-related tumours were observed in 2-year rat and mouse studies at oral doses up to 30 mg/kg/day in rats and 15 mg/kg/day in mice (8.9 and 30 times the recommended therapeutic exposures in humans based on plasma exposure to vorapaxar for rats and mice, respectively).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E468)
Povidone (E1201)
Magnesium stearate (E572)

Film coating
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Packs of 7, 28, 30 and 100 film-coated tablets in aluminium/aluminium blister cards.
Packs of 10 and 50 film-coated tablets in aluminium/aluminium unit-dose blister cards.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/976/001
EU/1/14/976/002
EU/1/14/976/003
EU/1/14/976/004
EU/1/14/976/005
EU/1/14/976/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:19 January 2015

10. DATE OF THE REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Schering-Plough Labo N.V.
Industriepark 30
BE-2220 Heist-op-den-Berg
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Zontivity 2 mg film-coated tablets
Vorapaxar

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.08 mg vorapaxar (as vorapaxar sulfate).

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
7 film-coated tablets
10 x 1 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 x 1 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/976/001	7 film-coated tablets
EU/1/14/976/002	10 x 1 film-coated tablets (unit-dose)
EU/1/14/976/003	28 film-coated tablets
EU/1/14/976/004	30 film-coated tablets
EU/1/14/976/005	50 x 1 film-coated tablets (unit-dose)
EU/1/14/976/006	100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zontivity

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zontivity 2 mg tablets
Vorapaxar

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER - unit dose

1. NAME OF THE MEDICINAL PRODUCT

Zontivity 2 mg tablets
Vorapaxar

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zontivity 2 mg film-coated tablets
vorapaxar

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zontivity is and what it is used for
2. What you need to know before you take Zontivity
3. How to take Zontivity
4. Possible side effects
5. How to store Zontivity
6. Contents of the pack and other information

1. What Zontivity is and what it is used for

What Zontivity is
Zontivity contains an active substance called vorapaxar, and it belongs to a group of medicines called 'anti-platelet medicines.'

Platelets are blood cells that help with normal blood clotting. Zontivity prevents platelets from sticking together. This reduces the chance of a blood clot forming and blocking the arteries, such as the arteries in the heart.

What Zontivity is used for
Zontivity is used in adults who have had a heart attack or have a condition known as "peripheral arterial disease" (also known as poor circulation in the legs).

Zontivity is used to lower your chance of:
- having another heart attack or stroke
- dying from a heart attack
- needing an urgent operation to open blocked arteries in the heart.

Your doctor will also give you instructions about acetylsalicylic acid or clopidogrel (other anti-platelet agents) that you may need to take with Zontivity.

2. What you need to know before you take Zontivity

Do not take Zontivity:
- if you have ever had a stroke or 'mini stroke' (also called a 'transient ischemic attack' or TIA)
- if you have had bleeding in the brain
- if you have unusual bleeding now, such as bleeding in your brain, stomach or gut
- if you are allergic to vorapaxar sulfate or any of the other ingredients of this medicine (listed in section 6)
- if you have severe liver disease

Do not take Zontivity if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Zontivity.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Zontivity if you:
- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery including dental surgery
- have ever had stomach ulcers or small growths in your gut ('colon polyps')
- have had recent bleeding from the stomach or gut
- have active peptic ulcer disease
- have liver or kidney problems
- have a bodyweight of less than 60 kg
- are over 75 years of age

If any of the above apply to you, or if you are not sure, talk to your doctor, pharmacist, or nurse before taking Zontivity.

Tell all of your doctors and dentists that you are taking Zontivity. They should talk to the doctor who prescribed Zontivity for you before you have any surgery or invasive procedure. Your doctor may advise stopping Zontivity before surgery.

If you have a stroke, 'mini-stroke', or bleeding in the brain while taking Zontivity, your doctor ought to stop your Zontivity. Follow your doctor's instructions about stopping Zontivity.

In general, use of anti-platelet medicines, older age, or a low body weight increase the risk of bleeding. Your doctor will decide if this medicine is appropriate for you.

Children and adolescents
Zontivity is not recommended for children and adolescents under 18 years of age. This is because it is not known if Zontivity is safe and works in children and adolescents.

Other medicines and Zontivity
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Zontivity may affect the way other medicines work, and other medicines may affect how Zontivity works. Do not take Zontivity if you are currently being treated with prasugrel or ticagrelor (other anti-platelet agents). If your doctor prescribes you prasugrel or ticagrelor, you should stop Zontivity and talk to your doctor.

It is especially important to tell your doctor if you take:
- itraconazole, ketoconazole, posaconazole (used to treat fungal infections)
- ritonavir, nelfinavir, indinavir, saquinavir (used to treat HIV-AIDS)
- boceprevir, telaprevir (used to treat hepatitis C virus infections)
- carbamazepine, phenytoin (anti-seizure medicines)
- clarithromycin, telithromycin (used to treat infections)
- rifampin (used to treat tuberculosis and some other infections)
- nefazodone (used to treat depression)

- antacids and pantoprazole (used to treat upset stomach)
- digoxin (used to treat heart failure)
- warfarin, other oral anticoagulants, heparin, or low molecular weight heparin (blood thinner medicines)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before taking this medicine.

It is not known if Zontivity will harm your unborn baby. You and your doctor will decide if you will take Zontivity.

Tell your doctor if you are breast-feeding. This is because it is not known if Zontivity passes into your breast milk. You and your doctor will decide if you will take Zontivity or breast-feed. You should not do both.

Driving and using machines
Zontivity is not likely to affect your ability to drive or use machines.

Zontivity and lactose
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor, pharmacist, or nurse before taking Zontivity.

3. How to take Zontivity

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet by mouth each day taken with or without food.

It may take at least 7 days for Zontivity to start working. Your doctor will determine if you should take Zontivity for more than 24 months.

Your doctor will determine if you should also take aspirin, clopidogrel, or both, while taking Zontivity.

If you take more Zontivity than you should
If you take more Zontivity than you are supposed to, talk to a doctor or go to hospital straight away. Take the medicine pack with you. You may be at increased risk of bleeding.

If you forget to take Zontivity
- If you forget a dose, take it as soon as you remember. However, if it is within 12 hours of the next dose, skip the missed dose.
- Do not take a double-dose (two doses at the same time) to make up for a forgotten dose.

If you stop taking Zontivity
- Do not stop taking Zontivity without first talking to the doctor who prescribed it for you.
- Take Zontivity on a regular basis and for as long as your doctor keeps prescribing it.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Call your doctor straight away if you have any of these symptoms of a stroke, which is uncommon:
- sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body
- sudden confusion, difficulty speaking,or understanding others
- sudden difficulty in walking or loss of balance or co-ordination
- suddenly feeling dizzy or sudden severe headache with no known cause

Severe bleeding is uncommon, but can be life threatening. Call your doctor straight away, if you have any of these signs or symptoms of bleeding while taking Zontivity:
- bleeding that is severe or that you cannot control
- unexpected bleeding or bleeding that lasts a long time
- pink, red, or brown urine
- vomiting blood or your vomit looks like 'coffee grounds'
- red or black stools (looks like tar)
- coughing up blood or blood clots

Other possible side effects

Common: may affect up to 1 in 10 people
- nose bleeds
- bruising

Uncommon: may affect up to 1 in 100 people
- low red blood cell count (anaemia)
- bleeding gums
- bleeding in your eye
- bleeding from cuts or wounds that is more than normal
- double vision
- inflammation of the stomach

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zontivity

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zontivity contains

- The active substance is vorapaxar sulfate. Each tablet contains 2.08 mg of vorapaxar (as vorapaxar sulfate).
- The other ingredients are:
  Tablet core: lactose monohydrate; cellulose microcrystalline (E460); croscarmellose sodium (E468); povidone (E1201); magnesium stearate (E572).

  Film-coating: lactose monohydrate; hypromellose (E464); titanium dioxide (E171); triacetin (E1518); iron oxide yellow (E172).

What Zontivity looks like and contents of the pack
Tablets are yellow, oval-shaped, film-coated tablets, size 8.48 mm x 4.76 mm, with "351" on one side and the MSD logo on the other side.

Pack sizes
Packs of 7, 28, 30 and 100 tablets in aluminium blister cards.
Packs of 10 and 50 tablets in aluminium unit-dose blister cards.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
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EN11 9BU
United Kingdom

Manufacturer
S-P Labo NV
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.