**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

**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
Hertfordshire
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:

**Belgique/België/Belgien**
MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38 693 (+32(0)27766211)
dpoc_belux@merck.com

**Lietuva**
UAB Merck Sharp & Dohme
Tel.: +370 5 278 02 47
msd_lietuva@merck.com

**България**
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@merck.com

**Luxembourg/Luxemburg**
MSD Belgium BVBA/SPRL
Tél/Tel: +32(0)27766211
dpoc_belux@merck.com

**Česká republika**
Merck Sharp & Dohme s.r.o.
Tel.: +420 233 010 111
dpoc_czechslovak@merck.com

**Magyarország**
MSD Pharma Hungary Kft.
Tel.: +361 888 53 00
hungary_msd@merck.com

**Danmark**
MSD Danmark ApS
Tlf: +45 4482 4000
dkmail@merck.com

**Malta**
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
malta_info@merck.com

**Deutschland**
MSD SHARP & DOHME GMBH
Tel: 0800 673 673 673 (+49 (0) 89 4561 2612)
e-mail@msd.de

**Eesti**
Merck Sharp & Dohme OÜ
Tel.: +372 6144 200
msdeesti@merck.com

**Ελλάδα**
MSD A.Φ.B.E.E.
Τηλ: +30 210 98 97 300
dpoc_greece@merck.com

**España**
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@merck.com

**France**
MSD France
Tél: + 33 (0) 1 80 46 40 40

**Hrvatska**
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 6611 333
croatia_info@merck.com

**Ireland**
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 299 8700
medinfo_ireland@merck.com

**Ísland**
Vistor hf.
Sími: +354 535 7000

**Italia**
MSD Italia S.r.l.
Tel: +39 06 361911
medicalinformation.it@merck.com

**Κύπρος**
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
cyprus_info@merck.com

**Latvija**
SIA Merck Sharp & Dohme Latvija
Tel: +371 67364224
msd_lv@merck.com.

**Nederland**
Merck Sharp & Dohme BV
Tel: 0800 9999000 (+31 23 5153153)
medicalinfo.nl@merck.com

**Norge**
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no

**Österreich**
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
msd-medizin@merck.com

**Polska**
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@merck.com

**Portugal**
Merck Sharp & Dohme, Lda
Tel: +351 21 4465700
clic@merck.com

**România**
Merck Sharp & Dohme Romania S.R.L.
Tel: +40 21 529 29 00
msdromania@merck.com

**Slovenija**
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: + 386 1 5204 201
msd_slovenia@merck.com

**Slovenská republika**
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@merck.com

**Suomi/Finland**
MSD Finland Oy
Puh/Tel: +358 (0) 9 804650
info@msd.fi

**Sverige**
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@merck.com

**United Kingdom**
Merck Sharp & Dohme Limited
Tel: +44 (0) 1992 467272
medicalinformationuk@merck.com

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