

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

Medicinal product no longer authorised

## 1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 75 mg of acetylsalicylic acid (ASA).

### Excipient with known effect:

Each film-coated tablet contains 102.6 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Yellow, film-coated capsule shaped tablets. The tablets have a length of 14.0 mm and a width of 6.8 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Clopidogrel/Acetylsalicylic acid Teva is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA).

Clopidogrel/Acetylsalicylic acid Teva is a fixed-dose combination medicinal product for continuation of therapy in:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy

For further information please refer to section 5.1.

### 4.2 Posology and method of administration

#### Posology

- Adults and elderly population

Clopidogrel/Acetylsalicylic acid Teva should be given as a single daily 75 mg/75 mg dose.

Clopidogrel/Acetylsalicylic acid Teva is used following initiation of therapy with clopidogrel and ASA given separately.

- *In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):* The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1). If the use of the combination of clopidogrel/acetylsalicylic acid is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.
- *In patients with ST segment elevation acute myocardial infarction:* Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the

combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1). If the use of the combination of clopidogrel/acetylsalicylic acid is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
  - For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.
- **Paediatric population**  
The safety and efficacy of clopidogrel/acetylsalicylic acid in children and adolescents under 18 years old have not been established. The combination of clopidogrel/acetylsalicylic acid is not recommended in this population.
  - **Renal impairment**  
The combination of clopidogrel/acetylsalicylic acid must not be used in patients with severe renal impairment (see section 4.3). Therapeutic experience is limited in patients with mild to moderate renal impairment (see section 4.4). Therefore, the combination of clopidogrel/acetylsalicylic acid should be used with caution in these patients.
  - **Hepatic impairment**  
The combination of clopidogrel/acetylsalicylic acid must not be used in patients with severe hepatic impairment (see section 4.3). Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4). Therefore, the combination of clopidogrel/acetylsalicylic acid should be used with caution in these patients.

#### Method of administration

For oral use.

It may be given with or without food.

### **4.3 Contraindications**

Due to the presence of both components of the medicinal product, Clopidogrel/Acetylsalicylic acid Teva is contraindicated in case of:

- Hypersensitivity to the active substances or to any of the excipients listed in section 2 or section 6.1.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

In addition, due to the presence of ASA, its use is also contraindicated in:

- Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
- Severe renal impairment.
- Third trimester of pregnancy (see section 4.6).

### **4.4 Special warnings and precautions for use**

#### *Bleeding and haematological disorders*

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As a dual antiplatelet agent, the combination of clopidogrel/acetylsalicylic acid should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in

patients receiving treatment with other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of the combination of clopidogrel/acetylsalicylic acid with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.5).

Patients should inform physicians and dentists that they are taking the combination of clopidogrel/acetylsalicylic acid before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for dual antiplatelet therapy should be reviewed and consideration given to the use of a single antiplatelet agent. If patients must temporarily stop antiplatelet therapy, the combination of clopidogrel/acetylsalicylic acid should be discontinued 7 days prior to surgery.

The combination of clopidogrel/acetylsalicylic acid prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should also be told that it might take longer than usual to stop bleeding when they take the combination of clopidogrel/acetylsalicylic acid, and that they should report any unusual bleeding (site or duration) to their physician.

#### *Thrombotic Thrombocytopenic Purpura (TTP)*

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

#### *Acquired haemophilia*

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and Clopidogrel/Acetylsalicylic acid should be discontinued.

#### *Recent transient ischaemic attack or stroke*

In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of ASA and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

#### *Cytochrome P450 2C19 (CYP2C19)*

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

#### *Cross-reactions among thienopyridines*

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or

haematological cross-reactions such as thrombocytopenia and neutropenia. Patients who have had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

#### *Caution required due to ASA*

- In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions
- In patients with gout since low doses of ASA increase urate concentrations.
- In children under 18 years of age, there is a possible association between ASA and Reye's syndrome. Reye's syndrome is a very rare disease which can be fatal.

#### *Gastrointestinal (GI)*

The combination of clopidogrel/acetylsalicylic acid should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper GI symptoms as this may be due to gastric ulceration which may lead to gastric bleeding. GI undesirable effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about the signs and symptoms of GI undesirable effects and what steps to take if they occur (see section 4.8).

#### *Excipients*

Clopidogrel/Acetylsalicylic acid Teva contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### *Oral anticoagulants*

The concomitant administration of the combination of clopidogrel/acetylsalicylic acid with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.4). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

#### *Glycoprotein IIb/IIIa inhibitors*

The combination of clopidogrel/acetylsalicylic acid should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

#### *Heparin*

In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between the combination of clopidogrel/acetylsalicylic acid and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

#### *Thrombolytics*

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8). The safety of the concomitant administration of the combination of clopidogrel/acetylsalicylic acid with other thrombolytic agents has not been formally established and should be undertaken with caution (see section 4.4).

### *NSAIDs*

In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs including Cox-2 inhibitors is not recommended (see section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

### *SSRIs*

Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

### *Other concomitant therapy with clopidogrel*

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see sections 4.4 and 5.2).

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

### *Proton Pump Inhibitors (PPI)*

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4).

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H<sub>2</sub> blockers (except cimetidine which is a CYP2C19 inhibitor) or antacids interfere with antiplatelet activity of clopidogrel.

Other medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic (PK) interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and

nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

#### *Other concomitant therapy with ASA*

Interactions with the following medicinal products have been reported with ASA:

#### *Uricosurics (benzbromarone, probenecid, sulfinpyrazone)*

Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

#### *Methotrexate*

Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with the combination of clopidogrel/acetylsalicylic acid as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

#### *Other interactions with ASA*

Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycemic agents.

#### *Other interactions with clopidogrel and ASA*

More than 30,000 patients entered into clinical trials with clopidogrel plus ASA at maintenance doses lower than or equal to 325 mg, and received a variety of concomitant medicinal products including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicinal product interaction information described above, interaction studies with the combination of clopidogrel/acetylsalicylic acid and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed.

## **4.6 Fertility, pregnancy and lactation**

### *Pregnancy*

No clinical data on exposure to the combination of clopidogrel/acetylsalicylic acid during pregnancy are available. The combination of clopidogrel/acetylsalicylic acid should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel/ASA.

Due to the presence of ASA, the combination of clopidogrel/acetylsalicylic acid is contraindicated during the third trimester of pregnancy.

### Clopidogrel:

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

ASA:

Low doses (up to 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100-500 mg/day:

There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in reproductive toxicity (see section 5.3). Until the 24<sup>th</sup> amenorrhea week (5<sup>th</sup> month of pregnancy), acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or until the 24<sup>th</sup> amenorrhea week (5<sup>th</sup> month of pregnancy), the dose should be kept as low and duration of treatment as short as possible.

From the beginning of the sixth month of pregnancy, all prostaglandin synthesis inhibitors may expose:

- the foetus to:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
- the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

#### *Breast-feeding*

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. ASA is known to be excreted in limited amounts in human milk. Breast-feeding should be discontinued during treatment with the combination of clopidogrel/acetylsalicylic acid.

#### *Fertility*

There are no fertility data with the combination of clopidogrel/acetylsalicylic acid. Clopidogrel was not shown to alter fertility in animal studies. It is unknown whether ASA alters fertility.

### **4.7 Effects on ability to drive and use machines**

The combination of clopidogrel/acetylsalicylic acid has no or negligible influence on the ability to drive and use machines.

### **4.8 Undesirable effects**

#### *Summary of the safety profile*

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in four major studies, the CAPRIE study (a study comparing clopidogrel alone to ASA) and the CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone) are

discussed below. Overall clopidogrel 75 mg/day was similar to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in the post-marketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was similar for clopidogrel and ASA.

In CURE there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the group taking ASA alone. The incidence of major bleeding was similar between groups. This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups.

*Tabulated list of adverse reactions*

Adverse reactions that occurred with clopidogrel alone, with ASA alone\* or with clopidogrel in combination with ASA either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare, not known</b>
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia, acquired haemophilia A.
Immune system disorders				Anaphylactic shock*, serum sickness, anaphylactoid reactions, aggravation of allergic symptoms of food allergy*, cross-reactive drug hypersensitivity

System Organ Class	Common	Uncommon	Rare	Very rare, not known
				among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*
Metabolism and nutrition disorders				Hypoglycaemia*, gout* (see section 4.4)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	Hearing loss* or tinnitus*
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid*, eosinophilic pneumonia.
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, gastro-duodenal ulcer/perforations*,

System Organ Class	Common	Uncommon	Rare	Very rare, not known
				<p>colitis (including ulcerative or lymphocytic colitis), upper gastro-intestinal symptoms* such as gastralgia (see section 4.4), stomatitis. Upper gastrointestinal disorders (oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis; gastro-duodenal ulcer/perforations)*; lower gastrointestinal disorders (small [jejunum and ileum] and large [colon and rectum] intestinal ulcers, colitis and intestinal perforation)*; upper gastro-intestinal symptoms* such as gastralgia (see section 4.4); these ASA-related GI reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patients with or without warning symptoms or a previous history of serious GI events*. Colitis (including ulcerative or lymphocytic colitis)</p>
Hepatobiliary disorders				<p>Acute liver failure, liver injury, mainly hepatocellular*, hepatitis, elevation of hepatic</p>

System Organ Class	Common	Uncommon	Rare	Very rare, not known
				enzymes*, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, drug induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Musculoskeletal and connective tissue disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)*, glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at the puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

\* Information reported in published information for ASA (frequency “not known”).

#### 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

There is no information concerning overdose with the combination of clopidogrel/acetylsalicylic acid.

Clopidogrel: Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

ASA: The following symptoms are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylates. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage.

The following symptoms can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 g. Plasma salicylate concentrations above 300 mg/l (1.67 mmol/l) suggest intoxication.

Non-cardiogenic pulmonary edema can occur with acute and chronic acetylsalicylic acid overdose (see section 4.8).

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalisating of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. Heparin, ATC Code: B01AC30.

#### *Mechanism of action*

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y<sub>12</sub> receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

#### *Pharmacodynamic effects*

Repeated doses of clopidogrel 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A<sub>2</sub>, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

#### *Clinical efficacy and safety*

The safety and efficacy of clopidogrel plus ASA have been evaluated in three double-blind studies involving over 61,900 patients: the CURE, CLARITY and COMMIT studies, comparing clopidogrel plus ASA to ASA alone, both treatments given in combination with other standard therapy.

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) plus ASA (75-325 mg once daily) or ASA alone (N=6,303), (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel plus ASA and ASA alone was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel plus ASA group and 719 (11.4%) in the ASA group, a 20% relative risk reduction (RRR) (95% CI of 10%-28%; p=0.00009) for the clopidogrel plus ASA group [17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)]. New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel plus ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

The use of clopidogrel in CURE was associated with a decrease in the need for thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel plus ASA group and 1,187 (18.8%) in the ASA group, a 14% relative risk reduction (95% CI of 6%-21%,  $p=0.0005$ ) for the clopidogrel plus ASA group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel plus ASA group and 363 (5.8%) in the ASA group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day,  $n=1,752$ ) plus ASA or ASA alone ( $n=1,739$ ), (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischARGE angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients  $\geq 65$  years. A total of 99.7% of patients received fibrinolytics (fibrin-specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel plus ASA group and 21.7% in the group treated with ASA alone reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favor of clopidogrel (95% CI: 24, 47%;  $p < 0.001$ ), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day,  $n=22,961$ ) plus ASA (162 mg/day), or ASA alone (162 mg/day) ( $n=22,891$ ), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients  $\geq 60$  years (26%  $\geq 70$  years) and 54.5% patients who received fibrinolytics.

Clopidogrel plus ASA significantly reduced the relative risk of death from any cause by 7% ( $p = 0.029$ ), and the relative risk of the combination of re-infarction, stroke or death by 9% ( $p = 0.002$ ), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

#### *Paediatric population*

The European Medicines Agency has waived the obligation to submit the results of studies with the combination of clopidogrel/acetylsalicylic acid in all subsets of the paediatric population in the treatment of coronary atherosclerosis (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

### Clopidogrel:

#### *Absorption*

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

#### *Distribution*

Clopidogrel and the main circulating (inactive) metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.

#### *Biotransformation*

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The  $C_{max}$  of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose.  $C_{max}$  occurs approximately 30 to 60 minutes after dosing.

#### *Elimination*

Following an oral dose of 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

#### *Pharmacogenetics*

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.

The CYP2C19\*1 allele corresponds to fully functional metabolism while the CYP2C19\*2 and CYP2C19\*3 alleles correspond to nonfunctional metabolism. The CYP2C19\*2 and CYP2C19\*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19\*4, \*5, \*6, \*7, and \*8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor

metabolisers with mean IPA (5  $\mu$ M ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Consistent with the above results, in a meta analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5  $\mu$ M ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

### Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

#### *Renal impairment*

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

#### *Hepatic impairment*

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

#### *Race*

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

### Acetylsalicylic acid (ASA):

#### *Absorption*

Following absorption, the ASA in the combination of clopidogrel/acetylsalicylic acid is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1.5-3 hours after dosing.

#### *Distribution*

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (<100 micrograms/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

#### *Biotransformation and Elimination*

The ASA in the combination of clopidogrel/acetylsalicylic acid is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in the combination of clopidogrel/acetylsalicylic acid has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged active substance depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid.

Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely

### **5.3 Preclinical safety data**

Clopidogrel: During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

Acetylsalicylic Acid: Single-dose studies have shown that the oral toxicity of ASA is low. Repeat-dose toxicity studies have shown that levels up to 200 mg/kg/day are well tolerated in rats; dogs appear to be more sensitive, probably due to the high sensitivity of canines to the ulcerogenic effects of NSAIDs. No genotoxicity or clastogenicity issues of concern have been found with ASA. Although no formal carcinogenicity studies have been performed with ASA, it has been shown that it is not a tumour promoter.

Reproduction toxicity data show that ASA is teratogenic in several laboratory animals.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core:

Lactose monohydrate  
Microcrystalline cellulose  
Hydroxypropylcellulose 100 cP  
Crospovidone (type A)  
Stearic Acid  
Croscarmellose sodium  
Hydrogenated vegetable oil  
Sodium lauril sulfate

#### Tablet coating:

Hypromellose 15 cP  
Polydextrose  
Titanium dioxide (E171)  
Quinoline yellow aluminium lake (E104)  
Talc  
Maltodextrin  
Medium chain triglycerides  
Iron oxide yellow (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

18 months.

After first opening bottle: 30 days

### **6.4 Special precautions for storage**

Do not store above 25°C.

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

### **6.5 Nature and contents of container**

Aluminium + Dessicant – Aluminium blisters. Pack sizes of 14, 28 and 30 film-coated tablets.  
White HDPE bottles and green polypropylene (PP) child-resistant closures with dessicant. Pack size of 30 film-coated tablets.  
White HDPE multi-layer bottles and green polypropylene (PP) child-resistant closures with dessicant.  
Pack size of 30 film-coated tablets.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

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

#### **7. MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

#### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/001-005

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:

#### **10. DATE OF 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>.

## 1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid (ASA).

### Excipient with known effect:

Each film-coated tablet contains 117.8 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light pink to pink, film-coated capsule shaped tablets. The tablets have a length of 14.0 mm and a width of 6.8 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Clopidogrel/Acetylsalicylic acid Teva is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA).

Clopidogrel/Acetylsalicylic acid Teva is a fixed-dose combination medicinal product for continuation of therapy in:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy

For further information please refer to section 5.1.

### 4.2 Posology and method of administration

#### Posology

- Adults and elderly population

Clopidogrel/Acetylsalicylic acid Teva should be given as a single daily 75 mg/100 mg dose.

Clopidogrel/Acetylsalicylic acid Teva is used following initiation of therapy with clopidogrel and ASA given separately.

- *In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):* The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1). If the use of the combination of clopidogrel/acetylsalicylic acid is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.
- *In patients with ST segment elevation acute myocardial infarction:* Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the

combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1). If the use of the combination of clopidogrel/acetylsalicylic acid is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
  - For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.
- **Paediatric population**  
The safety and efficacy of clopidogrel/acetylsalicylic acid in children and adolescents under 18 years old have not been established. The combination of clopidogrel/acetylsalicylic acid is not recommended in this population.
  - **Renal impairment**  
The combination of clopidogrel/acetylsalicylic acid must not be used in patients with severe renal impairment (see section 4.3). Therapeutic experience is limited in patients with mild to moderate renal impairment (see section 4.4). Therefore, the combination of clopidogrel/acetylsalicylic acid should be used with caution in these patients.
  - **Hepatic impairment**  
The combination of clopidogrel/acetylsalicylic acid must not be used in patients with severe hepatic impairment (see section 4.3). Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4). Therefore, the combination of clopidogrel/acetylsalicylic acid should be used with caution in these patients.

#### Method of administration

For oral use.

It may be given with or without food.

### **4.3 Contraindications**

Due to the presence of both components of the medicinal product, Clopidogrel/Acetylsalicylic acid Teva is contraindicated in case of:

- Hypersensitivity to the active substances or to any of the excipients listed in section 2 or section 6.1.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

In addition, due to the presence of ASA, its use is also contraindicated in:

- Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
- Severe renal impairment.
- Third trimester of pregnancy (see section 4.6).

### **4.4 Special warnings and precautions for use**

#### *Bleeding and haematological disorders*

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As a dual antiplatelet agent, the combination of clopidogrel/acetylsalicylic acid should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in

patients receiving treatment with other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of the combination of clopidogrel/acetylsalicylic acid with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.5).

Patients should inform physicians and dentists that they are taking the combination of clopidogrel/acetylsalicylic acid before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for dual antiplatelet therapy should be reviewed and consideration given to the use of a single antiplatelet agent. If patients must temporarily stop antiplatelet therapy, the combination of clopidogrel/acetylsalicylic acid should be discontinued 7 days prior to surgery.

The combination of clopidogrel/acetylsalicylic acid prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should also be told that it might take longer than usual to stop bleeding when they take the combination of clopidogrel/acetylsalicylic acid, and that they should report any unusual bleeding (site or duration) to their physician.

#### *Thrombotic Thrombocytopenic Purpura (TTP)*

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

#### *Acquired haemophilia*

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and Clopidogrel/Acetylsalicylic acid should be discontinued.

#### *Recent transient ischaemic attack or stroke*

In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of ASA and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

#### *Cytochrome P450 2C19 (CYP2C19)*

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

#### *Cross-reactions among thienopyridines*

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or

haematological cross-reactions such as thrombocytopenia and neutropenia. Patients who have had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

#### *Caution required due to ASA*

- In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions
- In patients with gout since low doses of ASA increase urate concentrations.
- In children under 18 years of age, there is a possible association between ASA and Reye's syndrome. Reye's syndrome is a very rare disease which can be fatal.

#### *Gastrointestinal (GI)*

The combination of clopidogrel/acetylsalicylic acid should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper GI symptoms as this may be due to gastric ulceration which may lead to gastric bleeding. GI undesirable effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about the signs and symptoms of GI undesirable effects and what steps to take if they occur (see section 4.8).

#### *Excipients*

Clopidogrel/Acetylsalicylic acid Teva contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### *Oral anticoagulants*

The concomitant administration of the combination of clopidogrel/acetylsalicylic acid with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.4). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

#### *Glycoprotein IIb/IIIa inhibitors*

The combination of clopidogrel/acetylsalicylic acid should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

#### *Heparin*

In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between the combination of clopidogrel/acetylsalicylic acid and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

#### *Thrombolytics*

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8). The safety of the concomitant administration of the combination of clopidogrel/acetylsalicylic acid with other thrombolytic agents has not been formally established and should be undertaken with caution (see section 4.4).

### *NSAIDs*

In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs including Cox-2 inhibitors is not recommended (see section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

### *SSRIs*

Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

### *Other concomitant therapy with clopidogrel*

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see sections 4.4 and 5.2).

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

### *Proton Pump Inhibitors (PPI)*

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4).

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H<sub>2</sub> blockers (except cimetidine which is a CYP2C19 inhibitor) or antacids interfere with antiplatelet activity of clopidogrel.

Other medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic (PK) interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and

nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

#### *Other concomitant therapy with ASA*

Interactions with the following medicinal products have been reported with ASA:

#### *Uricosurics (benzbromarone, probenecid, sulfinpyrazone)*

Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

#### *Methotrexate*

Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with the combination of clopidogrel/acetylsalicylic acid as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

#### *Other interactions with ASA*

Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycemic agents.

#### *Other interactions with clopidogrel and ASA*

More than 30,000 patients entered into clinical trials with clopidogrel plus ASA at maintenance doses lower than or equal to 325 mg, and received a variety of concomitant medicinal products including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicinal product interaction information described above, interaction studies with the combination of clopidogrel/acetylsalicylic acid and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed.

## **4.6 Fertility, pregnancy and lactation**

### *Pregnancy*

No clinical data on exposure to the combination of clopidogrel/acetylsalicylic acid during pregnancy are available. The combination of clopidogrel/acetylsalicylic acid should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel/ASA.

Due to the presence of ASA, the combination of clopidogrel/acetylsalicylic acid is contraindicated during the third trimester of pregnancy.

### Clopidogrel:

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

ASA:

Low doses (up to 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100-500 mg/day:

There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in reproductive toxicity (see section 5.3). Until the 24<sup>th</sup> amenorrhea week (5<sup>th</sup> month of pregnancy), acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or until the 24<sup>th</sup> amenorrhea week (5<sup>th</sup> month of pregnancy), the dose should be kept as low and duration of treatment as short as possible.

From the beginning of the sixth month of pregnancy, all prostaglandin synthesis inhibitors may expose:

- the foetus to:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
- the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

#### *Breast-feeding*

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. ASA is known to be excreted in limited amounts in human milk. Breast-feeding should be discontinued during treatment with the combination of clopidogrel/acetylsalicylic acid.

#### *Fertility*

There are no fertility data with the combination of clopidogrel/acetylsalicylic acid. Clopidogrel was not shown to alter fertility in animal studies. It is unknown whether ASA alters fertility.

### **4.7 Effects on ability to drive and use machines**

The combination of clopidogrel/acetylsalicylic acid has no or negligible influence on the ability to drive and use machines.

### **4.8 Undesirable effects**

#### *Summary of the safety profile*

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in four major studies, the CAPRIE study (a study comparing clopidogrel alone to ASA) and the CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone) are

discussed below. Overall clopidogrel 75 mg/day was similar to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in the post-marketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was similar for clopidogrel and ASA.

In CURE there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the group taking ASA alone. The incidence of major bleeding was similar between groups. This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups.

*Tabulated list of adverse reactions*

Adverse reactions that occurred with clopidogrel alone, with ASA alone\* or with clopidogrel in combination with ASA either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare, not known</b>
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia, acquired haemophilia A.
Immune system disorders				Anaphylactic shock*, serum sickness, anaphylactoid reactions, aggravation of allergic symptoms of food allergy*, cross-reactive drug hypersensitivity

System Organ Class	Common	Uncommon	Rare	Very rare, not known
				among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*
Metabolism and nutrition disorders				Hypoglycaemia*, gout* (see section 4.4)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	Hearing loss* or tinnitus*
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid*, eosinophilic pneumonia.
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, gastro-duodenal ulcer/perforations*,

System Organ Class	Common	Uncommon	Rare	Very rare, not known
				<p>colitis (including ulcerative or lymphocytic colitis), upper gastro-intestinal symptoms* such as gastralgia (see section 4.4), stomatitis. Upper gastrointestinal disorders (oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis; gastro-duodenal ulcer/perforations)*; lower gastrointestinal disorders (small [jejunum and ileum] and large [colon and rectum] intestinal ulcers, colitis and intestinal perforation)*; upper gastro-intestinal symptoms* such as gastralgia (see section 4.4); these ASA-related GI reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patients with or without warning symptoms or a previous history of serious GI events*. Colitis (including ulcerative or lymphocytic colitis)</p>
Hepatobiliary disorders				<p>Acute liver failure, liver injury, mainly hepatocellular*, hepatitis, elevation of hepatic</p>

System Organ Class	Common	Uncommon	Rare	Very rare, not known
				enzymes*, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, drug induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Musculoskeletal and connective tissue disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)*, glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at the puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

\* Information reported in published information for ASA (frequency “not known”).

#### 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

There is no information concerning overdose with the combination of clopidogrel/acetylsalicylic acid.

Clopidogrel: Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

ASA: The following symptoms are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylates. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage.

The following symptoms can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 g. Plasma salicylate concentrations above 300 mg/l (1.67 mmol/l) suggest intoxication.

Non-cardiogenic pulmonary edema can occur with acute and chronic acetylsalicylic acid overdose (see section 4.8).

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalisating of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. Heparin, ATC Code: B01AC30.

#### *Mechanism of action*

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y<sub>12</sub> receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

#### *Pharmacodynamic effects*

Repeated doses of clopidogrel 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A<sub>2</sub>, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

#### *Clinical efficacy and safety*

The safety and efficacy of clopidogrel plus ASA have been evaluated in three double-blind studies involving over 61,900 patients: the CURE, CLARITY and COMMIT studies, comparing clopidogrel plus ASA to ASA alone, both treatments given in combination with other standard therapy.

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) plus ASA (75-325 mg once daily) or ASA alone (N=6,303), (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel plus ASA and ASA alone was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel plus ASA group and 719 (11.4%) in the ASA group, a 20% relative risk reduction (RRR) (95% CI of 10%-28%; p=0.00009) for the clopidogrel plus ASA group [17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)]. New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel plus ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

The use of clopidogrel in CURE was associated with a decrease in the need for thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel plus ASA group and 1,187 (18.8%) in the ASA group, a 14% relative risk reduction (95% CI of 6%-21%,  $p=0.0005$ ) for the clopidogrel plus ASA group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel plus ASA group and 363 (5.8%) in the ASA group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day,  $n=1,752$ ) plus ASA or ASA alone ( $n=1,739$ ), (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischARGE angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients  $\geq 65$  years. A total of 99.7% of patients received fibrinolytics (fibrin-specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel plus ASA group and 21.7% in the group treated with ASA alone reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favor of clopidogrel (95% CI: 24, 47%;  $p < 0.001$ ), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day,  $n=22,961$ ) plus ASA (162 mg/day), or ASA alone (162 mg/day) ( $n=22,891$ ), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients  $\geq 60$  years (26%  $\geq 70$  years) and 54.5% patients who received fibrinolytics.

Clopidogrel plus ASA significantly reduced the relative risk of death from any cause by 7% ( $p = 0.029$ ), and the relative risk of the combination of re-infarction, stroke or death by 9% ( $p = 0.002$ ), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

#### *Paediatric population*

The European Medicines Agency has waived the obligation to submit the results of studies with the combination of clopidogrel/acetylsalicylic acid in all subsets of the paediatric population in the treatment of coronary atherosclerosis (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

### Clopidogrel:

#### *Absorption*

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

#### *Distribution*

Clopidogrel and the main circulating (inactive) metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.

#### *Biotransformation*

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The  $C_{max}$  of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose.  $C_{max}$  occurs approximately 30 to 60 minutes after dosing.

#### *Elimination*

Following an oral dose of 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

#### *Pharmacogenetics*

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.

The CYP2C19\*1 allele corresponds to fully functional metabolism while the CYP2C19\*2 and CYP2C19\*3 alleles correspond to nonfunctional metabolism. The CYP2C19\*2 and CYP2C19\*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19\*4, \*5, \*6, \*7, and \*8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor

metabolisers with mean IPA (5  $\mu$ M ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Consistent with the above results, in a meta analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5  $\mu$ M ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

### Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

#### *Renal impairment*

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

#### *Hepatic impairment*

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

#### *Race*

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

### Acetylsalicylic acid (ASA):

#### *Absorption*

Following absorption, the ASA in the combination of clopidogrel/acetylsalicylic acid is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1.5-3 hours after dosing.

#### *Distribution*

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (<100 micrograms/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

#### *Biotransformation and Elimination*

The ASA in the combination of clopidogrel/acetylsalicylic acid is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in the combination of clopidogrel/acetylsalicylic acid has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged active substance depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid.

Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely

### **5.3 Preclinical safety data**

Clopidogrel: During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

Acetylsalicylic Acid: Single-dose studies have shown that the oral toxicity of ASA is low. Repeat-dose toxicity studies have shown that levels up to 200 mg/kg/day are well tolerated in rats; dogs appear to be more sensitive, probably due to the high sensitivity of canines to the ulcerogenic effects of NSAIDs. No genotoxicity or clastogenicity issues of concern have been found with ASA. Although no formal carcinogenicity studies have been performed with ASA, it has been shown that it is not a tumour promoter.

Reproduction toxicity data show that ASA is teratogenic in several laboratory animals.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core:

Lactose monohydrate  
Microcrystalline cellulose  
Hydroxypropylcellulose 100 cP  
Crospovidone (type A)  
Stearic Acid  
Croscarmellose sodium  
Hydrogenated vegetable oil  
Sodium lauril sulfate

#### Tablet coating:

Hypromellose 15 cP  
Polydextrose  
Titanium dioxide (E171)  
Talc  
Maltodextrin  
Medium chain triglycerides  
Iron oxide yellow (E172)  
Carmine (E120)  
Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

18 months.

After first opening bottle: 30 days

### **6.4 Special precautions for storage**

Do not store above 25°C.

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

### **6.5 Nature and contents of container**

Aluminium + Dessicant – Aluminium blisters. Pack sizes of 10, 14, 28, 30, 50, 90 and 100 film-coated tablets.

White HDPE bottles and green polypropylene (PP) child-resistant closures with dessicant. Pack size of 30 film-coated tablets.

White HDPE multi-layer bottles and green polypropylene (PP) child-resistant closures with dessicant. Pack size of 30 film-coated tablets.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

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

#### **7. MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 52031 GA Haarlem  
The Netherlands

#### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/006-014

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:

#### **10. DATE OF 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

Merckle GmbH  
Ludwig-Merckle-Strasse 3  
D-89143 Blaubeuren-Weiler  
Germany

Pliva Croatia Ltd  
Prilaz baruna Filipovica 25  
10 000 Zagreb  
Croatia

TEVA Czech Industries s.r.o.  
Ostravská 29, č.p. 305, Opava - Komárov, -  
747 70,  
Czech Republic

TEVA UK Limited  
BRAMPTON ROAD  
HAMPDEN PARK  
EASTBOURNE,  
EAST SUSSEX, BN22 9AG,  
United Kingdom

Teva Operations Poland Sp. z o.o.  
ul. Mogilska 80.  
31-546, Krakow  
Poland

Teva Pharma B.V.  
Swensweg 5  
NL-2031 GA Haarlem  
The Netherlands

Teva Pharmaceutical Works Private Limited Company  
Pallagi út 13  
HU-4042 Debrecen  
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **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 marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article

107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Medicinal product no longer authorised

Medicinal product no longer authorised

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

Medicinal product no longer authorised

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON for blisters**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg film-coated tablets  
Clopidogrel/Acetylsalicylic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 75 mg of acetylsalicylic acid.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

14 film-coated tablets  
28 film-coated tablets  
30 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**

Do not store above 25°C.  
Store in the original package in order to protect from light and moisture.

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

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 52031 GA Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/001-003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg tablets  
Clopidogrel/Acetylsalicylic acid

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Medicinal product no longer authorised

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON for bottles**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg film-coated tablets  
Clopidogrel/Acetylsalicylic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 75 mg of acetylsalicylic acid.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 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

After first opening bottle use within 30 days.

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

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

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

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/004-005

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Clpidogrel/Acetylsalicylic acid Teva 75 mg/75 mg

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg film-coated tablets  
Clopidogrel/Acetylsalicylic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 75 mg of acetylsalicylic acid.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 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

After first opening bottle use within 30 days.

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Store in the original package in order to protect from light and 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**

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/004-005

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Medicinal product no longer authorised

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON for blisters**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg film-coated tablets  
Clopidogrel/Acetylsalicylic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

10 film-coated tablets  
14 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
50 film-coated tablets  
90 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**

Do not store above 25°C.

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

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

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/006-012

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Clodogrel/Acetylsalicylic acid Teva 75 mg/100 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg tablets  
Clopidogrel/Acetylsalicylic acid

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Medicinal product no longer authorised

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON for bottles**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg film-coated tablets  
Clopidogrel/Acetylsalicylic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 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

After first opening bottle use within 30 days.

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

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

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

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/013-014

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Clpidogrel/Acetylsalicylic acid Teva 75 mg/100 mg

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg film-coated tablets  
Clopidogrel/Acetylsalicylic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 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

After first opening bottle use within 30 days.

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Store in the original package in order to protect from light and 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**

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/942/013-014

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Medicinal product no longer authorised

Medicinal product no longer authorised

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg film-coated tablets clopidogrel/acetylsalicylic acid

**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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4. .

#### What is in this leaflet

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

#### 1. What Clopidogrel/Acetylsalicylic acid Teva is and what it is used for

Clopidogrel/Acetylsalicylic acid Teva contains clopidogrel and acetylsalicylic acid (ASA) and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping in some types of blood vessels (called arteries), antiplatelet medicinal products reduce the chances of blood clots forming (a process called atherothrombosis).

Clopidogrel/Acetylsalicylic acid Teva is taken by adults to prevent blood clots forming in hardened arteries which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Clopidogrel/Acetylsalicylic acid Teva in place of the two separate medicines, clopidogrel and ASA, to help prevent blood clots because you have experienced a severe type of chest pain known as 'unstable angina' or heart attack (myocardial infarction). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow.

#### 2. What you need to know before you take Clopidogrel/Acetylsalicylic acid Teva

##### Do not take Clopidogrel/Acetylsalicylic acid Teva

- If you are allergic to clopidogrel, acetylsalicylic acid (ASA) or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to other products called non-steroidal anti-inflammatory products usually used to treat painful and/or inflammatory conditions of muscles or joints.
- If you have a medical condition that include the combination of asthma, nasal discharge (runny nose) and polyps (a type of growth in the nose).
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- If you suffer from severe liver disease.
- If you suffer from severe kidney disease.
- If you are in your last trimester of pregnancy

## Warnings and precautions

If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel/Acetylsalicylic acid Teva:

- if you have a risk of bleeding such as:
  - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer).
  - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body).
  - a recent serious injury.
  - a recent surgery (including dental).
  - a planned surgery (including dental) in the next seven days.
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred in the last seven days.
- if you have kidney or liver disease.
- if you have a history of asthma or allergic reactions including allergy to any medicine used to treat your disease.
- if you have gout.

While you are taking Clopidogrel/Acetylsalicylic acid Teva:

- You should tell your doctor
  - if a surgery (including dental) is planned.
  - if you have any stomach or abdominal pain or bleeding in the stomach or bowels (red stools or black stools).
- You should also **tell your doctor immediately** if you develop a medical condition (also known as Thrombotic Thrombocytopenic Purpura or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 'Possible side effects').
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should **contact your doctor straightaway** (see section 4 'Possible side effects').
- Your doctor may order blood tests.

### Children and adolescents

Clopidogrel/Acetylsalicylic acid Teva is not intended for use in children or adolescents less than 18 years of age. There is a possible association between acetylsalicylic acid (ASA) and Reye's Syndrome when products containing ASA are given to children or adolescents with a viral infection. Reye's Syndrome is a very rare disease which can be fatal.

### Other medicines and Clopidogrel/Acetylsalicylic acid Teva

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some other medicines may influence the use of Clopidogrel/Acetylsalicylic acid Teva or vice versa.

You should specifically tell your doctor if you take

- oral anticoagulants, medicines used to reduce blood clotting,
- ASA or another non-steroidal anti-inflammatory medicine usually used to treat painful and/or inflammatory conditions of muscle or joints,
- heparin or any other injectable medicine used to reduce blood clotting,
- omeprazole, esomeprazole or cimetidine, medicines to treat upset stomach,
- methotrexate, a medicine used to treat severe joint disease (rheumatoid arthritis) or skin disease (psoriasis),
- probenecid, benzbromarone, or sulfapyrazone, medicines used to treat gout,
- fluconazole, voriconazole, ciprofloxacin, or chloramphenicol, medicines to treat bacterial and fungal infections,

- fluoxetine, fluvoxamine, or moclobemide, medicines to treat depression,
- carbamazepine, or oxcarbazepine, medicines to treat some forms of epilepsy,
- ticlopidine, other antiplatelet agent.

You **should stop** other clopidogrel treatment while you are taking Clopidogrel/Acetylsalicylic acid Teva.

An occasional use of ASA (no more than 1,000 mg in any 24-hour period) should generally not cause a problem, but prolonged use of ASA in other circumstances should be discussed with your doctor or pharmacist.

### **Pregnancy and breast-feeding**

Do **NOT** take Clopidogrel/Acetylsalicylic acid Teva during third trimester of pregnancy. It is preferable not to take this product during first and second trimesters of pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel/Acetylsalicylic acid Teva. If you become pregnant while taking Clopidogrel/Acetylsalicylic acid Teva, **consult your doctor immediately** as it is recommended not to take Clopidogrel/Acetylsalicylic acid Teva while you are pregnant.

You **should not** breast-feed while using this medicine.

If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

### **Driving and using machines**

Clopidogrel/Acetylsalicylic acid Teva should not affect your ability to drive or to use machines.

### **Clopidogrel/Acetylsalicylic acid Teva contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

## **3. How to take Clopidogrel/Acetylsalicylic acid Teva**

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 of Clopidogrel/Acetylsalicylic acid Teva per day, to be taken orally with a glass of water, with or without food.

You should take your medicine at the same time each day.

Depending on your condition, your doctor will determine the length of time for which you need to take Clopidogrel/Acetylsalicylic acid Teva. If you have had a heart attack, it should be prescribed for at least four weeks. In any case, you should take it for as long as your doctor continues to prescribe it.

### **If you take more Clopidogrel/Acetylsalicylic acid Teva than you should**

**Contact your doctor or the nearest hospital emergency department immediately** because of the increased risk of bleeding.

### **If you forget to take Clopidogrel/Acetylsalicylic acid Teva**

If you forget to take a dose of Clopidogrel/Acetylsalicylic acid Teva, but remember within 12 hours of your usual time, take your tablet straight away and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

### **If you stop taking Clopidogrel/Acetylsalicylic acid Teva**

**Do not stop the treatment unless your doctor tells you so.** Contact your doctor or pharmacist before stopping.

If you have been told by your doctor to stop treatment temporarily, ask your doctor when to restart the treatment.

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

## **4. Possible side effects**

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

### **Contact your doctor immediately if you experience:**

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots, and/or confusion (see section 2 ‘Warnings and precautions’).
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

**The most common side effect which has been seen with Clopidogrel/Acetylsalicylic acid Teva is bleeding.** Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

### **If you experience prolonged bleeding when taking Clopidogrel/Acetylsalicylic acid Teva**

If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, **you should contact your doctor straightaway** (see section 2 ‘Warnings and precautions’).

### **Other side effects include:**

#### **Common side effects (may affect up to 1 in 10 people):**

- diarrhoea
- abdominal pain
- indigestion or heartburn.

#### **Uncommon side effects (may affect up to 1 in 100 people):**

- headache
- stomach ulcer
- vomiting (being sick)
- nausea (feeling sick)
- constipation
- excessive gas in stomach or intestines
- rashes
- itching
- dizziness
- sensation of tingling and numbness.

#### **Rare side effect (may affect up to 1 in 1000 people):**

- vertigo.

#### **Very rare side effects (may affect up to 1 in 10,000 people):**

- jaundice
- burning in stomach and/or oesophagus
- severe abdominal pain with or without back pain
- fever
- breathing difficulties sometimes associated with cough
- generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting)
- swelling in the mouth
- blisters of the skin
- skin allergy
- sore mouth (stomatitis)
- decrease in blood pressure
- confusion
- hallucinations
- joint pain
- muscular pain
- changes in taste of foods
- inflammation of small vessels.

**Side effects with unknown frequency (frequency cannot be estimated from the available data):**

- ulcer perforation
- ringing in the ears
- hearing loss
- sudden life-threatening allergic reactions
- kidney disease
- low blood sugar
- gout (a condition of painful, swollen joints caused by uric acid crystals)
- worsening of food allergies.

In addition, your doctor may identify changes in your blood or urine tests.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. 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 Clopidogrel/Acetylsalicylic acid Teva**

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, bottle and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

After first opening the bottle use within 30 days.

Do not use this medicine if you notice any visible signs of deterioration

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 Clopidogrel/Acetylsalicylic acid Teva contains**

- The active substances are clopidogrel and acetylsalicylic acid. Each tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 75 mg of acetylsalicylic acid.
- The other ingredients are:
  - Tablet core: lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose 100 cP, crospovidone (type A), stearic acid, croscarmellose sodium, hydrogenated vegetable oil and sodium lauril sulfate.
  - Tablet coating: hypromellose, polydextrose, titanium dioxide (E171), quinoline yellow aluminium lake (E104), talc, maltodextrin, medium chain triglycerides and iron oxide yellow (E172).

### **What Clopidogrel/Acetylsalicylic acid Teva looks like and contents of the pack**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/75 mg film-coated tablets are yellow, film-coated capsule shaped tablets. The tablets have a length of 14.0 mm and a width of 6.8 mm.

Clopidogrel/Acetylsalicylic acid Teva is supplied in blisters in pack sizes of 14, 28 and 30 film-coated tablets or in bottles in a pack size of 30 film-coated tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

Manufacturers:

TEVA Pharmaceutical Works Private Limited Company  
Pallagi út 13  
4042 Debrecen  
Hungary

TEVA UK Ltd  
Brampton Road  
Hampden Park  
Eastbourne  
East Sussex, BN22 9AG  
United Kingdom

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

Teva Czech Industries s.r.o.  
Ostravska 29, c.p. 305  
74770 Opava-Komarov  
Czech Republic

Teva Operations Poland Sp. z o.o.  
ul. Mogilska 80  
31-546 Krakow  
Poland

Merckle GmbH  
Ludwig-Merckle-Straße 3  
89143 Blaubeuren  
Germany

Pliva Croatia Ltd  
Prilaz baruna Filipovica 25  
10 000 Zagreb  
Croatia

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

**België/Belgique/Belgien**

Teva Pharma Belgium N.V./S.A./AG  
Tel/Tél: +32 3 820 73 73

**България**

Тева Фармасютикълс България ЕООД  
Тел: +359 2 489 95 82

**Česká republika**

Teva Pharmaceuticals CR, s.r.o.  
Tel: +420 251 007 111

**Danmark**

Teva Denmark A/S  
Tlf: +45 44 98 55 11

**Deutschland**

Teva GmbH  
Tel: +49 731 402 08

**Eesti**

Teva Eesti esindus UAB Sicor Biotech Eesti filiaal  
Tel: +372 661 0801

**Ελλάδα**

Teva Ελλάς Α.Ε.  
Τηλ: +30 210 72 79 099

**España**

Teva Pharma S.L.U.  
Tél: +34 91 387 32 80

**France**

Teva Santé  
Tél: +33 1 55 91 7800

**Hrvatska**

Pliva Hrvatska d.o.o  
Tel: + 385 1 37 20 000

**Lietuva**

UAB "Sicor Biotech"  
Tel: +370 5 266 02 03

**Luxembourg/Luxemburg**

Teva Pharma Belgium N.V./S.A./AG  
Tel/Tél: +32 3 820 73 73

**Magyarország**

Teva Gyógyszergyár Zrt  
Tel.: +36 1 288 64 00

**Malta**

Teva Pharmaceuticals Ireland  
Tel: +353 51 321740

**Nederland**

Teva Nederland B.V.  
Tel: +31 800 0228 400

**Norge**

Teva Norway AS  
Tlf: +47 6677 55 90

**Österreich**

ratiopharm Arzneimittel Vertriebs GmbH  
Tel: +43 1 97007 0

**Polska**

Teva Pharmaceuticals Polska Sp. z o.o.  
Tel.: +48 22 345 93 00

**Portugal**

Teva Pharma - Produtos Farmacêuticos Lda  
Tel: +351 21 476 75 50

**România**

Teva Pharmaceuticals S.R.L  
Tel: +4021 230 6524

**Ireland**

Teva Pharmaceuticals Ireland  
Tel: +353 51 321 740

**Ísland**

ratiopharm Oy  
Sími: +358 20 180 5900

**Italia**

Teva Italia S.r.l.  
Tel: +39 028 917 981

**Κύπρος**

Teva Ελλάς A.E.  
Τηλ: +30 210 72 79 099

**Latvija**

UAB Sicor Biotech filiāle Latvijā  
Tel: +371 67 323 666

**Slovenija**

Pliva Ljubljana d.o.o.  
Tel: +386 1 58 90 390

**Slovenská republika**

Teva Pharmaceuticals Slovakia s.r.o.  
Tel: +421 2 5726 7911

**Suomi/Finland**

ratiopharm Oy  
Puh/Tel: +358 20 180 5900

**Sverige**

Teva Sweden AB  
Tel: +46 42 12 11 00

**United Kingdom**

Teva UK Limited  
Tel: +44 1977 628 500

**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>.

Medicinal product no longer authorised

## Package leaflet: Information for the user

### Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg film-coated tablets clopidogrel/acetylsalicylic acid

**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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4. .

#### What is in this leaflet

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

#### 1. What Clopidogrel/Acetylsalicylic acid Teva is and what it is used for

Clopidogrel/Acetylsalicylic acid Teva contains clopidogrel and acetylsalicylic acid (ASA) and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping in some types of blood vessels (called arteries), antiplatelet medicinal products reduce the chances of blood clots forming (a process called atherothrombosis).

Clopidogrel/Acetylsalicylic acid Teva is taken by adults to prevent blood clots forming in hardened arteries which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Clopidogrel/Acetylsalicylic acid Teva in place of the two separate medicines, clopidogrel and ASA, to help prevent blood clots because you have experienced a severe type of chest pain known as 'unstable angina' or heart attack (myocardial infarction). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow.

#### 2. What you need to know before you take Clopidogrel/Acetylsalicylic acid Teva

##### Do not take Clopidogrel/Acetylsalicylic acid Teva

- If you are allergic to clopidogrel, acetylsalicylic acid (ASA) or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to other products called non-steroidal anti-inflammatory products usually used to treat painful and/or inflammatory conditions of muscles or joints.
- If you have a medical condition that include the combination of asthma, nasal discharge (runny nose) and polyps (a type of growth in the nose).
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- If you suffer from severe liver disease.
- If you suffer from severe kidney disease.
- If you are in your last trimester of pregnancy

## Warnings and precautions

If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel/Acetylsalicylic acid Teva:

- if you have a risk of bleeding such as:
  - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer).
  - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body).
  - a recent serious injury.
  - a recent surgery (including dental).
  - a planned surgery (including dental) in the next seven days.
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred in the last seven days.
- if you have kidney or liver disease.
- if you have a history of asthma or allergic reactions including allergy to any medicine used to treat your disease.
- if you have gout.

While you are taking Clopidogrel/Acetylsalicylic acid Teva:

- You should tell your doctor
  - if a surgery (including dental) is planned.
  - if you have any stomach or abdominal pain or bleeding in the stomach or bowels (red stools or black stools).
- You should also **tell your doctor immediately** if you develop a medical condition (also known as Thrombotic Thrombocytopenic Purpura or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 ‘Possible side effects’).
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should **contact your doctor straightaway** (see section 4 ‘Possible side effects’).
- Your doctor may order blood tests.

### Children and adolescents

Clopidogrel/Acetylsalicylic acid Teva is not intended for use in children or adolescents less than 18 years of age. There is a possible association between acetylsalicylic acid (ASA) and Reye’s Syndrome when products containing ASA are given to children or adolescents with a viral infection. Reye’s Syndrome is a very rare disease which can be fatal.

### Other medicines and Clopidogrel/Acetylsalicylic acid Teva

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some other medicines may influence the use of Clopidogrel/Acetylsalicylic acid Teva or vice versa.

You should specifically tell your doctor if you take

- oral anticoagulants, medicines used to reduce blood clotting,
- ASA or another non-steroidal anti-inflammatory medicine usually used to treat painful and/or inflammatory conditions of muscle or joints,
- heparin or any other injectable medicine used to reduce blood clotting,
- omeprazole, esomeprazole or cimetidine, medicines to treat upset stomach,
- methotrexate, a medicine used to treat severe joint disease (rheumatoid arthritis) or skin disease (psoriasis),
- probenecid, benzbromarone, or sulfapyrazone, medicines used to treat gout,
- fluconazole, voriconazole, ciprofloxacin, or chloramphenicol, medicines to treat bacterial and fungal infections,

- fluoxetine, fluvoxamine, or moclobemide, medicines to treat depression,
- carbamazepine, or oxcarbazepine, medicines to treat some forms of epilepsy,
- ticlopidine, other antiplatelet agent.

You **should stop** other clopidogrel treatment while you are taking Clopidogrel/Acetylsalicylic acid Teva.

An occasional use of ASA (no more than 1,000 mg in any 24-hour period) should generally not cause a problem, but prolonged use of ASA in other circumstances should be discussed with your doctor or pharmacist.

### **Pregnancy and breast-feeding**

Do **NOT** take Clopidogrel/Acetylsalicylic acid Teva during third trimester of pregnancy. It is preferable not to take this product during first and second trimesters of pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel/Acetylsalicylic acid Teva. If you become pregnant while taking Clopidogrel/Acetylsalicylic acid Teva, **consult your doctor immediately** as it is recommended not to take Clopidogrel/Acetylsalicylic acid Teva while you are pregnant.

You **should not** breast-feed while using this medicine.

If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

### **Driving and using machines**

Clopidogrel/Acetylsalicylic acid Teva should not affect your ability to drive or to use machines.

### **Clopidogrel/Acetylsalicylic acid Teva contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

## **3. How to take Clopidogrel/Acetylsalicylic acid Teva**

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 of Clopidogrel/Acetylsalicylic acid Teva per day, to be taken orally with a glass of water, with or without food.

You should take your medicine at the same time each day.

Depending on your condition, your doctor will determine the length of time for which you need to take Clopidogrel/Acetylsalicylic acid Teva. If you have had a heart attack, it should be prescribed for at least four weeks. In any case, you should take it for as long as your doctor continues to prescribe it.

### **If you take more Clopidogrel/Acetylsalicylic acid Teva than you should**

**Contact your doctor or the nearest hospital emergency department immediately** because of the increased risk of bleeding.

### **If you forget to take Clopidogrel/Acetylsalicylic acid Teva**

If you forget to take a dose of Clopidogrel/Acetylsalicylic acid Teva, but remember within 12 hours of your usual time, take your tablet straight away and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

### **If you stop taking Clopidogrel/Acetylsalicylic acid Teva**

**Do not stop the treatment unless your doctor tells you so.** Contact your doctor or pharmacist before stopping.

If you have been told by your doctor to stop treatment temporarily, ask your doctor when to restart the treatment.

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

## **4. Possible side effects**

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

### **Contact your doctor immediately if you experience:**

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots, and/or confusion (see section 2 ‘Warnings and precautions’).
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

**The most common side effect which has been seen with Clopidogrel/Acetylsalicylic acid Teva is bleeding.** Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

### **If you experience prolonged bleeding when taking Clopidogrel/Acetylsalicylic acid Teva**

If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, **you should contact your doctor straightaway** (see section 2 ‘Warnings and precautions’).

### **Other side effects include:**

#### **Common side effects (may affect up to 1 in 10 people):**

- diarrhoea
- abdominal pain
- indigestion or heartburn.

#### **Uncommon side effects (may affect up to 1 in 100 people):**

- headache
- stomach ulcer
- vomiting (being sick)
- nausea (feeling sick)
- constipation
- excessive gas in stomach or intestines
- rashes
- itching
- dizziness
- sensation of tingling and numbness.

#### **Rare side effect (may affect up to 1 in 1000 people):**

- vertigo.

#### **Very rare side effects (may affect up to 1 in 10,000 people):**

- jaundice
- burning in stomach and/or oesophagus
- severe abdominal pain with or without back pain
- fever
- breathing difficulties sometimes associated with cough
- generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting)
- swelling in the mouth
- blisters of the skin
- skin allergy
- sore mouth (stomatitis)
- decrease in blood pressure
- confusion
- hallucinations
- joint pain
- muscular pain
- changes in taste of foods
- inflammation of small vessels.

**Side effects with unknown frequency (frequency cannot be estimated from the available data):**

- ulcer perforation
- ringing in the ears
- hearing loss
- sudden life-threatening allergic reactions
- kidney disease
- low blood sugar
- gout (a condition of painful, swollen joints caused by uric acid crystals)
- worsening of food allergies.

In addition, your doctor may identify changes in your blood or urine tests.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. 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 Clopidogrel/Acetylsalicylic acid Teva**

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, bottle and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

After first opening the bottle use within 30 days.

Do not use this medicine if you notice any visible signs of deterioration

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 Clopidogrel/Acetylsalicylic acid Teva contains**

- The active substances are clopidogrel and acetylsalicylic acid.  
Each tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid.
- The other ingredients are:
  - Tablet core: lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose 100 cP, crospovidone (type A), stearic acid, croscarmellose sodium, hydrogenated vegetable oil and sodium lauril sulfate.
  - Tablet coating: hypromellose, polydextrose, titanium dioxide (E171), talc, maltodextrin, medium chain triglycerides, iron oxide yellow (E172), carmine (E120), iron oxide red (E172).

### **What Clopidogrel/Acetylsalicylic acid Teva looks like and contents of the pack**

Clopidogrel/Acetylsalicylic acid Teva 75 mg/100 mg film-coated tablets are light pink to pink, film-coated capsule shaped tablets. The tablets have a length of 14.0 mm and a width of 6.8 mm.

Clopidogrel/Acetylsalicylic acid Teva is supplied in blisters in pack sizes of 10, 14, 28, 30, 50, 90 and 100 film-coated tablets or in bottles in a pack size of 30 film-coated tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

Manufacturers:

TEVA Pharmaceutical Works Private Limited Company  
Pallagi út 13  
4042 Debrecen  
Hungary

TEVA UK Ltd  
Brampton Road  
Hampden Park  
Eastbourne  
East Sussex, BN22 9AG  
United Kingdom

Teva Pharma B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

Teva Czech Industries s.r.o.  
Ostravska 29, c.p. 305  
74770 Opava-Komarov  
Czech Republic

Teva Operations Poland Sp. z o.o.  
ul. Mogilska 80  
31-546 Krakow  
Poland

Merckle GmbH  
Ludwig-Merckle-Straße 3  
89143 Blaubeuren  
Germany

Pliva Croatia Ltd  
Prilaz baruna Filipovica 25  
10 000 Zagreb  
Croatia

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

**België/Belgique/Belgien**

Teva Pharma Belgium N.V./S.A./AG  
Tel/Tél: +32 3 820 73 73

**България**

Тева Фармасютикълс България ЕООД  
Тел: +359 2 489 95 82

**Česká republika**

Teva Pharmaceuticals CR, s.r.o.  
Tel: +420 251 007 111

**Danmark**

Teva Denmark A/S  
Tlf: +45 44 98 55 11

**Deutschland**

Teva GmbH  
Tel: +49 731 402 08

**Eesti**

Teva Eesti esindus UAB Sicor Biotech Eesti filiaal  
Tel: +372 661 0801

**Ελλάδα**

Teva Ελλάς Α.Ε.  
Τηλ: +30 210 72 79 099

**España**

Teva Pharma S.L.U.  
Tél: +34 91 387 32 80

**France**

Teva Santé  
Tél: +33 1 55 91 7800

**Hrvatska**

Pliva Hrvatska d.o.o  
Tel: + 385 1 37 20 000

**Lietuva**

UAB "Sicor Biotech"  
Tel: +370 5 266 02 03

**Luxembourg/Luxemburg**

Teva Pharma Belgium N.V./S.A./AG  
Tel/Tél: +32 3 820 73 73

**Magyarország**

Teva Gyógyszergyár Zrt  
Tel.: +36 1 288 64 00

**Malta**

Teva Pharmaceuticals Ireland  
Tel: +353 51 321740

**Nederland**

Teva Nederland B.V.  
Tel: +31 800 0228 400

**Norge**

Teva Norway AS  
Tlf: +47 6677 55 90

**Österreich**

ratiopharm Arzneimittel Vertriebs GmbH  
Tel: +43 1 97007 0

**Polska**

Teva Pharmaceuticals Polska Sp. z o.o.  
Tel.: +48 22 345 93 00

**Portugal**

Teva Pharma - Produtos Farmacêuticos Lda  
Tel: +351 21 476 75 50

**România**

Teva Pharmaceuticals S.R.L  
Tel: +4021 230 6524

**Ireland**

Teva Pharmaceuticals Ireland  
Tel: +353 51 321 740

**Ísland**

ratiopharm Oy  
Sími: +358 20 180 5900

**Italia**

Teva Italia S.r.l.  
Tel: +39 028 917 981

**Κύπρος**

Teva Ελλάς A.E.  
Τηλ: +30 210 72 79 099

**Latvija**

UAB Sicor Biotech filiāle Latvijā  
Tel: +371 67 323 666

**Slovenija**

Pliva Ljubljana d.o.o.  
Tel: +386 1 58 90 390

**Slovenská republika**

Teva Pharmaceuticals Slovakia s.r.o.  
Tel: +421 2 5726 7911

**Suomi/Finland**

ratiopharm Oy  
Puh/Tel: +358 20 180 5900

**Sverige**

Teva Sweden AB  
Tel: +46 42 12 11 00

**United Kingdom**

Teva UK Limited  
Tel: +44 1977 628 500

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

Medicinal product no longer authorised