

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

*Medicinal product no longer authorised*

## 1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrobromide).

### Excipients with known effect:

Each tablet contains 62.16 mg lactose monohydrate and 10 mg hydrogenated castor oil.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Light pink to pink, capsule-shaped film-coated tablets debossed with "C75" on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### *Prevention of atherothrombotic events*

Clopidogrel is indicated in:

- Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- Adult patients suffering from acute coronary syndrome:
  - 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, in combination with acetylsalicylic acid (ASA)
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

#### *Prevention of atherothrombotic and thromboembolic events in atrial fibrillation*

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

For further information please refer to section 5.1.

### 4.2 Posology and method of administration

Posology:

- Adults and older people

Clopidogrel should be given as a single daily dose of 75 mg.

In patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300-mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. 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).
- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300-mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined 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).

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel (see section 5.1).

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  
Clopidogrel should not be used in children because of efficacy concerns (see section 5.1)
- Renal impairment  
Therapeutic experience is limited in patients with renal impairment (see section 4.4).
- Hepatic impairment  
Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

Method of administration  
For oral use  
It may be given with or without food.

#### **4.3 Contraindications**

- Hypersensitivity to the active substance 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.

#### **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 with other antiplatelet agents, clopidogrel 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 ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs). 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 clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel 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 be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), 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 should be discontinued.

#### *Recent ischaemic stroke*

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

#### *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 thienopyridines (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 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.

#### *Renal impairment*

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section 4.2).

#### *Hepatic impairment*

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

#### *Excipients*

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

This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

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

*Oral anticoagulants:* the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (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:* clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

*Acetylsalicylic acid (ASA):* ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

*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 clopidogrel 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).

*NSAIDs:* in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

*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:* 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 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.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

## 4.6 Fertility, pregnancy and lactation

### *Pregnancy*

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).

### *Breast-feeding*

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel Teva Pharma B.V.

### *Fertility*

Clopidogrel was not shown to alter fertility in animal studies.

## 4.7 Effects on ability to drive and use machines

Clopidogrel 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 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY, COMMIT and ACTIVE-A studies are discussed below. 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 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 placebo plus ASA group. 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.

In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel

+ ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo +ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

*Tabulated list of adverse reactions*

Adverse reactions that occurred 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 drug 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, acquired haemophilia A, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (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)		



<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare, not known*</b>
Ear and labyrinth disorders			Vertigo	
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, 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, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, 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

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

\* Information related to clopidogrel with 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

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.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04.

##### *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 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.

#### *Clinical efficacy and safety*

The safety and efficacy of clopidogrel have been evaluated in 5 double-blind studies involving over 88,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT and ACTIVE-A studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4];  $p=0.045$ ), which corresponds, for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at  $p=0.003$ ) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR=23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR=7.3%; CI: -5.7 to 18.7 [ $p=0.258$ ]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR=-4.0%; CI: -22.5 to 11.7 [ $p=0.639$ ]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients  $\leq 75$  years.

Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

#### *Acute coronary syndrome*

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) or placebo (N=6,303), both given in combination with ASA (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 and placebo 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-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%;  $p=0.00009$ ) for the clopidogrel-treated 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 + 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 of 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-treated group and 1,187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%,  $p=0.0005$ ) for the clopidogrel-treated group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated 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.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

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,  $n=1,752$ ) or placebo ( $n=1,739$ ), both in combination with ASA (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 group and 21.7% in the placebo group 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,  $n=22,961$ ) or placebo ( $n=22,891$ ), in combination with ASA (162 mg/day), 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 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.

#### *Atrial fibrillation*

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.

The ACTIVE-A study ( $N=7,554$ ) was a multicenter, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA ( $N=3,772$ ) to placebo + ASA ( $N=3,782$ ). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age  $\geq 75$  years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction  $< 45\%$ ; or documented peripheral vascular disease. The mean CHADS2 score was 2.0 (range 0-6).

The major exclusion criteria for patients were documented peptic ulcer disease within the previous 6 months; prior intracerebral hemorrhage; significant thrombocytopenia (platelet count  $< 50 \times 10^9/l$ ); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

Seventy-three percent (73%) of patients enrolled into the ACTIVE-A study were unable to take VKA due to physician assessment, inability to comply with INR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk of bleeding; for 26% of the patients, the physician's decision was based on the patient's unwillingness to take VKA.

The patient population included 41.8 % women. The mean age was 71 years, 41.6% of patients were  $\geq 75$  years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group (relative risk reduction of 11.1%; 95% CI of 2.4% to 19.1%;  $p=0.013$ ), primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA (relative risk reduction, 28.4%; 95% CI, 16.8% to 38.3%;  $p=0.00001$ ).

### *Paediatric population*

In a dose escalation study of 86 neonates or infants up to 24 months of age at risk for thrombosis (PICOLO), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kg in neonates and infants and 0.15 mg/kg only in neonates. The dose of 0.2 mg/kg achieved the mean percent inhibition of 49.3% (5  $\mu\text{M}$  ADP-induced platelet aggregation) which was comparable to that of adults taking clopidogrel 75 mg/day.

In a randomised, double-blind, parallel-group study (CLARINET), 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomised to receive clopidogrel 0.2 mg/kg ( $n=467$ ) or placebo ( $n=439$ ) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac-related intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group) (see section 4.2). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups. In the long-term safety follow-up of this study, 26 patients with the shunt still in place at one year of age received clopidogrel up to 18 months of age. No new safety concerns were noted during this long-term follow-up.

The CLARINET and the PICOLO trials were conducted using a constituted solution of clopidogrel. In a relative bioavailability study in adults, the constituted solution of clopidogrel showed a similar extent and slightly higher rate of absorption of the main circulating (inactive) metabolite compared to the authorised tablet

## **5.2 Pharmacokinetic properties**

### *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<sub>max</sub> 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<sub>max</sub> occurs approximately 30 to 60 minutes after dosing.

#### *Elimination*

Following an oral dose of <sup>14</sup>C-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 are nonfunctional. 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 (ultrarapid, 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 ultrarapid, 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 μM 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 μM 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.

### **5.3 Preclinical safety data**

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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### *Tablet core*

Lactose monohydrate  
Cellulose, microcrystalline  
Hydroxypropylcellulose (E463)  
Crospovidone (type A)  
Hydrogenated castor oil  
Sodium laurilsulfate

#### *Film-coating*

Lactose monohydrate  
Hypromellose (E464)  
Titanium dioxide (E171)  
Macrogol 4000  
Iron oxide red (E172)  
Iron oxide yellow (E172)  
Indigo carmine aluminium lake (E132)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months

For the HDPE bottle presentation chemical and physical in-use stability have been demonstrated for:

- 30 tablets bottle: 30 days
- 100 tablets bottle: 100 days

Any remaining tablets should be discarded at the end of this period.

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

Do not store above 25°C.

Store in the original package to protect from light.

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

Aluminium-aluminium peelable perforated unit-dose blisters, aluminium-aluminium perforated unit dose blisters and HDPE bottles with polypropylene closures or child resistant polypropylene closures and silica gel desiccant.

- Peelable perforated blisters contain 14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 film-coated tablet.

- Perforated blisters contain 14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 film-coated tablet.
- Bottles contain 30 or 100 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.  
Computerweg 10  
3542 DR Utrecht  
The Netherlands

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

EU/1/10/649/001-016

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

16.06.2011

#### **10. DATE OF REVISION OF THE TEXT**

<DD month YYYY>

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

Medicinal product no longer authorised

**ANNEX II**

- A. MANUFACTURER 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**

Medicinal product no longer authorised

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

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

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

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

Pharmachemie B.V.  
Swensweg 5  
2031 GA Haarlem  
The Netherlands

TEVA Santé SA  
Rue Bellocier  
89107 Sens  
France

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 periodic safety update reports 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)

Not applicable.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

Medicinal product no longer authorised

**A. LABELLING**

Medicinal product no longer authorised

## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON of peelable blisters (14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 film-coated tablet)**

### 1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets  
clopidogrel

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

Each film-coated tablet contains 75 mg clopidogrel (as hydrobromide)

### 3. LIST OF EXCIPIENTS

It also contains lactose and hydrogenated castor oil. See leaflet for further information

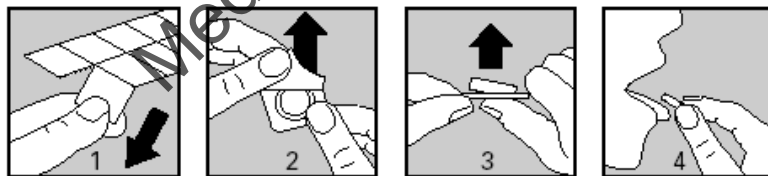
### 4. PHARMACEUTICAL FORM AND CONTENTS

14x1 film-coated tablet  
28x1 film-coated tablet  
30x1 film-coated tablet  
50x1 film-coated tablet  
84x1 film-coated tablet  
90x1 film-coated tablet  
100x1 film-coated tablet

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.



Separate one individual blister cell from the rest of the strip by gently tearing along the perforations around it.

Carefully peel off the backing

Push the tablet out

Put the tablet in your mouth and swallow with water or another liquid.

### 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 to protect from light.

**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**

Teva Pharma B.V.  
Computerweg 10  
3542 DR Utrecht  
The Netherlands

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Clopidogrel Teva Pharma B.V. 75 mg



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

**BLISTER (14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 film-coated tablets)**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets  
clopidogrel

**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 of blisters (14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 film-coated tablet)**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets  
clopidogrel

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

Each film-coated tablet contains 75 mg clopidogrel (as hydrobromide)

**3. LIST OF EXCIPIENTS**

It also contains lactose and hydrogenated castor oil. See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

14x1 film-coated tablet  
28x1 film-coated tablet  
30x1 film-coated tablet  
50x1 film-coated tablet  
84x1 film-coated tablet  
90x1 film-coated tablet  
100x1 film-coated tablet

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before 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 to protect from light.

**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**

Teva Pharma B.V.  
Computerweg 10  
3542 DR Utrecht  
The Netherlands

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Clopidogrel Teva Pharma B.V. 75 mg

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

**BLISTER (14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 film-coated tablet)**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets  
clopidogrel

**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 of bottles (30 or 100 film-coated tablets)**

**1. NAME OF THE MEDICINAL PRODUCT**

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets  
clopidogrel

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

Each film-coated tablet contains 75 mg clopidogrel (as hydrobromide)

**3. LIST OF EXCIPIENTS**

It also contains lactose and hydrogenated castor oil. See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

30 film-coated tablets  
100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before 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

30 tablets HDPE bottle:  
Discard 30 days after first opening

100 tablets HDPE bottle:  
Discard 100 days after first opening

**9. SPECIAL STORAGE CONDITIONS**

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

**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**

Teva Pharma B.V.  
Computerweg 10  
3542 DR Utrecht  
The Netherlands

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Clopidogrel Teva Pharma B.V. 75 mg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING**

**BOTTLE LABEL (30 or 100 film-coated tablets)**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets  
clopidogrel  
oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

30 tablets HDPE bottle:  
Discard 30 days after first opening

100 tablets HDPE bottle:  
Discard 100 days after first opening

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

30 film-coated tablets  
100 film-coated tablets

**6. OTHER**

**B. PACKAGE LEAFLET**

Medicinal product no longer authorised



## Package leaflet: Information for the user

### Clopidogrel Teva Pharma B.V. 75 mg film-coated tablets clopidogrel

**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 have any side effects, including any side effects not listed in this leaflet, talk your doctor or pharmacist. See section 4

#### What is in this leaflet

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

#### 1. What Clopidogrel Teva Pharma B.V. is and what it is used for

Clopidogrel Teva Pharma B.V. contains clopidogrel and belongs to a group of medicines called “platelet aggregation inhibitors.” It works by stopping certain particles in your blood (“platelets”) from sticking together to form blood clots which can block blood flow to important parts of your body including your heart and your brain.

If you suffer from hardening of the arteries (“atherosclerosis”) there is an increased risk of a blood clot forming in your blood vessels. In adults Clopidogrel Teva Pharma B.V. reduces the risk of blood clots forming which in turn reduces the risk of serious conditions such as heart attack and stroke from occurring.

You have been prescribed Clopidogrel Teva Pharma B.V. because:

- You have hardening of the arteries and have recently suffered from a heart attack, a stroke or have a condition known as “peripheral arterial disease” (diseases of the blood vessels except those in the brain and heart).
- You have experienced a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. You should also be given acetylsalicylic acid (a substance used to relieve pain and lower fever as well as to prevent blood clotting) by your doctor.
- You have an irregular heartbeat, a condition called ‘atrial fibrillation’, and you cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Clopidogrel Teva Pharma B.V. and acetylsalicylic acid for this condition. Your doctor should have prescribed Clopidogrel Teva Pharma B.V. plus acetylsalicylic acid if you cannot take ‘oral anticoagulants’ and you do not have a risk of major bleeding.

## 2. What you need to know before you take Clopidogrel Teva Pharma B.V.

### Do not take Clopidogrel Teva Pharma B.V.

- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of this medicine (listed in section 6).
- If you have severe liver disease.
- If you are suffering from another condition which is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- If you think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Clopidogrel Teva Pharma B.V.

### Warnings and precautions

Tell your doctor before you start to take this medicine if:

- You are at increased risk of bleeding. For example:
  - If you have recently suffered from a serious injury
  - If you have recently undergone surgery or are due to have surgery (including dental surgery)
  - If you have any blood disorder which makes internal bleeding (bleeding inside your body) more likely
  - If you suffer from any other illness which makes internal bleeding more likely (e.g. stomach ulcers or wounds inside the eye)
- You have had a clot in an artery of your brain (ischaemic stroke) which occurred within the last seven days
- You have liver or kidney disease.
- You have had an allergy or reaction to any medicine used to treat your disease.

While you are taking Clopidogrel Teva Pharma B.V.:

- You should tell your doctor if surgery (including dental) is planned
- You should also tell your doctor immediately if you develop a medical condition (known as Thrombotic Thrombocytopenic Purpura) that includes altered behaviour, headaches, coma, visual disturbances, seizures (fitting), kidney failure, fever, extreme tiredness, weakness or bleeding into the stomach, bowels or skin (including small red spots or large bruised areas) (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

Do not give this medicine to children because it does not work.

### Other medicines and Clopidogrel Teva Pharma B.V.

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

Talk to your doctor if you are using or have recently used any of the following medicines:

- Oral anticoagulants (oral medicines used to stop blood clotting) such as warfarin. Their use with Clopidogrel Teva Pharma B.V. is not recommended.
- Glycoprotein IIb/IIIa inhibitors (medicines used to stop blood clotting). E.g. abciximab, eptifibatide or tirofiban.
- Heparin (medicine used to prevent blood clotting).

- Medicines used to break down blood clots (e.g. alteplase and streptokinase).
- Non-steroidal anti-inflammatory medicines (used to treat painful inflammatory conditions of the joints or muscles). E.g. ibuprofen, diclofenac and meloxicam.
- Omeprazole, esomeprazole or cimetidine, medicines to treat upset stomach.
- Fluconazole, voriconazole, ciprofloxacin, or chloramphenicol, medicines to treat bacterial and fungal infections.
- Carbamazepine, or oxcarbazepine, medicines to treat some forms of epilepsy.
- Ticlopidine, other antiplatelet agent.
- a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
- moclobemide, medicine to treat depression.

Taking these medicines in combination with Clopidogrel Teva Pharma B.V. could result in an increased risk of bleeding.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed clopidogrel in combination with acetylsalicylic acid, a substance used to relieve pain and lower fever. An occasional use of acetylsalicylic acid (no more than 1,000 mg in any 24 hour period) should generally not cause a problem, but prolonged use in other circumstances should be discussed with your doctor.

#### **Clopidogrel Teva Pharma B.V. with food and drink**

You can take Clopidogrel Teva Pharma B.V. with or without food.

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

It is preferable not to use this medicine during pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel Teva Pharma B.V. If you become pregnant while taking Clopidogrel Teva Pharma B.V., consult your doctor immediately as it is recommended not to take clopidogrel while you are pregnant.

You should not breastfeed while taking this medicine.

If you are breastfeeding or planning to breastfeed, talk to your doctor before taking this medicine.

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

#### **Driving and using machines**

Clopidogrel Teva Pharma B.V. is unlikely to affect your ability to drive or operate machinery.

#### **Clopidogrel Teva Pharma B.V. contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

**Clopidogrel Teva Pharma B.V. contains hydrogenated castor oil.** This may cause stomach upset and diarrhoea.

### **3. How to take Clopidogrel Teva Pharma B.V.**

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 75 mg tablet per day which should be swallowed with water or another liquid. You should take your medicine regularly at the same time each day. You can take it with or without food.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Clopidogrel Teva Pharma B.V. once at the start of treatment. Then, the usual dose is one 75-mg tablet of Clopidogrel Teva Pharma B.V. per day

You should continue taking Clopidogrel Teva Pharma B.V. for as long as your doctor has told you to take it.

#### **If you take more Clopidogrel Teva Pharma B.V. than you should**

If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. An overdose is likely to cause an increased risk of bleeding. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

#### **If you forget to take Clopidogrel Teva Pharma B.V.**

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

If you forget to take a dose of Clopidogrel Teva Pharma B.V., but don't remember within 12 hours of the missed dose, skip the missed dose and take the next tablet at the usual time. Do not take a double dose to make up for a forgotten tablet.

#### **If you stop taking Clopidogrel Teva Pharma B.V.**

Do not stop taking Clopidogrel Teva Pharma B.V. without discussing it with your doctor first.

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.

Some of the side effects may be serious. If you suffer from any of the following symptoms you should contact your doctor immediately:

- Fever, signs of infection (e.g. sore throat), pale skin or extreme tiredness. These may be due to a decrease of some blood cells
- Altered behaviour, headaches, coma, visual disturbances, seizures (fitting), kidney failure, fever, extreme tiredness, weakness or bleeding into the stomach, bowels or skin (including small red spots or large bruised areas). This could indicate that you are suffering from a serious condition called thrombotic thrombocytopenic purpura (rare disorder of the blood clotting system which causes multiple blood clots to form around the body)
- Signs of liver problems such as yellowing of the skin and whites of 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, itching and blistering of the skin. These may be the signs of an allergic reaction.

#### **Bleeding**

The most common side effect (affects 1 to 10 users in 100) reported for medicines containing clopidogrel is bleeding. Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleeds or blood in the urine. In a small

number of cases, bleeding in the eye, inside the head, the abdomen, the lung and the joints have also been reported.

If you cut or injure yourself, it may take slightly longer than usual for bleeding to stop. This is linked to the way that your medicine works. For minor cuts and injuries (e.g. shaving cuts) you should not worry. However, if you are in any doubt, bleeding becomes serious or you experience unexpected bleeding from unusual parts of your body you should contact your doctor straight away (see section 2 'Warnings and precautions').

The following side effects have been reported.

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

- Bruising, haematoma (unusual bleeding under the skin), nose bleeds, bleeding in the stomach or bowels, increased bleeding at the site of a puncture wound
- Diarrhoea, abdominal pain, indigestion or heartburn

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

Headache and dizziness

Prolonged bleeding, bleeding inside the head, bleeding in the eye, blood in the urine and/or purpura (red spots on the skin caused by bleeding underneath the skin)

Rashes, itching, abnormal touch sensation

Ulcers in the stomach and small intestine, nausea, vomiting, constipation, flatulence (wind) and inflammation of the stomach leading to sickness, loss of appetite and discomfort after eating

Reduction in blood platelets which makes bleeding or bruising more likely

Blood disorders including a reduction in the number of white blood cells which makes infections more likely.

Rare side effects (may affect up to 1 in 1000 people):

Reduced levels of certain white blood cells which increases the risk of infection (neutropenia)

Vertigo (dizziness accompanied by a whirling sensation)

Bleeding inside the abdomen

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

A serious condition called thrombotic thrombocytopenic purpura (rare disorder of the blood clotting system which causes multiple blood clots to form around the body). Symptoms may include altered behaviour, headaches, coma, visual disturbances, seizures (fitting), kidney failure, fever, extreme tiredness, weakness, or bleeding into the stomach, bowels or skin (including small red spots or large bruised areas)

Severe reduction in certain blood cells leading to increased risk of bleeding or bruising, increased risk of infections, pale skin and extreme tiredness

Generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting), breathing difficulties, swelling or inflammation of the mouth, skin allergy, blisters on the skin

Confusion or hallucinations

Taste disorders

Sore mouth (stomatitis)

Inflammation of the blood vessels, decrease in blood pressure

Yellowing of the skin and whites of the eyes (jaundice)

Bleeding in the lungs, throat, stomach or bowels, abdomen or joints

Bleeding of post-operative wounds or other serious bleeds

Severe abdominal pain with or without back pain, pain in the joints and muscular pain

Diarrhoea

Fever

Changes in levels of certain substances in your blood or urine. This may be detectable via 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 Teva Pharma B.V.**

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 outer carton, bottle or 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 to protect from light.

30 tablets HDPE bottles:

Discard any remaining tablets 30 days after first opening of the bottle.

100 tablets HDPE bottles:

Discard any remaining tablets 100 days after first opening of the bottle.

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 to protect the environment.

### **6. Contents of the pack and other information**

#### **What Clopidogrel Teva Pharma B.V. contains**

The active substance is clopidogrel. Each film-coated tablet contains 75 mg of clopidogrel (as hydrobromide).

The other ingredients in the tablet core are (see section 2 ‘Clopidogrel Teva Pharma B.V. contains lactose’ and ‘Clopidogrel Teva Pharma B.V. contains hydrogenated castor oil’) lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose (E463), croscopovidone (type A), hydrogenated castor oil and sodium laurilsulfate, and in the film-coating are lactose monohydrate, hypromellose (E464), titanium dioxide (E171), macrogol 4000, iron oxide red (E172), iron oxide yellow (E172), indigo carmine aluminium lake (E132).

#### **What Clopidogrel Teva Pharma B.V. looks like and contents of the pack**

The film-coated tablets are light pink to pink, film coated, capsule shaped tablets. One side of the tablet is debossed with “C75”. The other side of the tablet is plain.

Clopidogrel Teva Pharma B.V. is supplied in peelable perforated blisters of aluminium/ aluminium containing 14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 tablet; perforated blisters of aluminium/ aluminium containing 14x1, 28x1, 30x1, 50x1, 84x1, 90x1 or 100x1 tablet or HDPE bottles with polypropylene closures or child resistant polypropylene closures and silica gel desiccant containing 30 or 100 tablets.

Not all pack sizes may be marketed.

Please note that instructions on how to remove the tablet from the blister strip are given on the outer carton of the peelable blisters.

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

Marketing Authorisation Holder:

Teva Pharma B.V.,

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Manufacturer:

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Detailed information is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.